COMMUNICABLE DISEASE APPLIED EPIDEMIOLOGY IN QUEENSLAND

Thesis for the degree of Master of Philosophy (Applied Epidemiology)

Jonathan Andrew Malo

Communicable Diseases Branch

Queensland Health

2016–2017

Stephen Lambert

Field Supervisor

Kerri Viney & Stephanie Davis

Academic Supervisors

Queensland Government

Australian National University

Originality statement

I hereby declare that this submission is my own work and to the best of my knowledge it contains no materials previously published or written by another person, or substantial proportions of material which have been accepted for the award of any other degree or diploma at ANU or any other educational institution, except where due acknowledgement is made in the text. Any contribution made to the research by others, with whom I have worked is explicitly acknowledged in the thesis. I also declare that the intellectual content of this thesis is the product of my own work, except to the extent that assistance from others in the project's design and conception or in style, presentation, or linguistic expression is acknowledged.

Jonathan Andrew Malo

09 November 2017

Whenever I'm about to do something, I think "would an idiot do that?"
And if they would, I do not do that thing.

—Dwight K Schrute

Acknowledgements

I gratefully acknowledge and give many thanks to the contributions and support of my supervisors, colleagues, friends, and family to my MAE journey.

Stephen—for coercing me into selecting the Queensland MAE placement (I know you will say there was no coercion but that is how I am choosing to remember it). You helped ensure the work I was doing was useful and allowed me to take control of my projects. Your brains and wit made you a formidable adversary during our intellectual debates, which I look forward to continuing—and triumphing—in the future.

Stephanie—for providing me with advice even before I commenced the MAE program. Your feedback always caused me to think and reflect more thoroughly about my projects and their importance to public health.

Kerri—for coming in at the end and providing me with supervision while on the other side of the world. It was a great pleasure working with you on Ebeye and you provided me with great support while I was there.

Fellow MAEs—for enhancing the journey and making course blocks enjoyable.

Friends—for keeping me sane with other activities and adventures.

Domino and Frankie—for sticking with me and allowing me to pursue my goals with unwavering support.

Cayley—for being a great sister and providing me with free messages. You now know what an epidemiologist is.

Mum—for giving me the brains to do this.

Dad—for giving me the drive and stubbornness to continue pushing myself and achieving goals.

Table of contents

Abbreviations

7vPCV	7-valent pneumococcal conjugate vaccine
10vPCV	10-valent pneumococcal conjugate vaccine
13vPCV	13-valent pneumococcal conjugate vaccine
23vPPV	23-valent pneumococcal polysaccharide vaccine
ABS	Australian Bureau of Statistics
ALT	Alanine transaminase
ARF	Acute rheumatic fever
ATAGI	Australian Technical Advisory Group on Immunisation
AUSLAB	Queensland Pathology laboratory results software program
CAP	Community-acquired pneumonia
CDB	Communicable Diseases Branch, Queensland Health
CDNA	Communicable Diseases Network Australia
CI	Confidence interval
CRF	Case report form
DHHS	Department of Health and Human Services, Victoria
EIPDSWG	Enhanced invasive pneumococcal disease surveillance working group
HCV	Hepatitis C virus
HR	Hazard ratio
IDU	Injecting drug use
IPD	Invasive pneumococcal disease
LRT	Likelihood ratio test
MSPHU	Metro South Public Health Unit
NIP	National Immunisation Program
NOCS	Notifiable Conditions System
NNDSS	National Notifiable Diseases Surveillance System
PCV	Pneumococcal conjugate vaccine
PHU	Public health unit
PPE	Personal protective equipment
PWID	People who inject drugs
QFSS	Queensland Forensic and Scientific Services
RHD	Rheumatic heart disease
VIVAS	Vaccine Information and Vaccine Administration System
VT	Vaccine-type
WHO	World Health Organization
WHS	Workplace health and safety
WPRO	World Health Organization Western Pacific Regional Office

Abstract

The Communicable Diseases Branch (CDB) of Queensland Health has the role of protecting the health of Queenslanders through the monitoring, surveillance, and control of communicable diseases. From February 2016 to December 2017, I undertook a field placement within the CDB. This thesis details projects undertaken during this 22-month field placement. The projects comprise an investigation of a Q fever outbreak at an animal refuge clinic and veterinary clinic, the establishment of a surveillance system to identify newly acquired hepatitis C infections in Queensland, an analysis of vaccine breakthrough invasive pneumococcal disease in Queensland in children younger than 5 years of age, and an analysis of the risk of recurrent invasive pneumococcal disease in Queensland. Also described in this thesis are other public health experiences gained during my placement, including my role in teaching, an assessment of the need to include rheumatic heart disease as a notifiable condition in Queensland, a WHO Western Pacific Regional Office consultancy, and a lookback investigation of a dental clinic. Together, these projects and experiences fulfil the core requirements of the Master of Philosophy (Applied Epidemiology) program at Australian National University.

(This page is otherwise blank)

I

Introduction to field placement and summary of experience

Field placement overview

My placement for the duration of the MAE program was at the Communicable Diseases Branch (CDB) within the Prevention Division of Queensland Health, located in Brisbane. Three units exist within the CDB: Blood Borne Viruses and Sexually Transmissible Infections, Communicable Diseases and Infection Management, and Epidemiology and Research.

The main responsibilities of the CDB include:

- protecting the public health of Queenslanders from communicable diseases;
- overseeing legislation, policy, and operational management related to communicable diseases;
- developing advice and guidelines for preventing communicable diseases spreading from person to person and from animals to people;
- coordinating Queensland's immunisation program;
- monitoring and coordinating the response to disease outbreaks attributed to communicable diseases;
- planning for and responding to emerging pandemics and biosecurity threats; and
- surveillance of notifiable conditions.

The public health system in Queensland operates as a decentralised system, with 13 public health units (PHUs) across the state. PHUs are responsible for the public health management of notifiable conditions within their respective jurisdictions.

My primary role was within the Epidemiology and Research unit, but worked with other units as required by the projects I was undertaking. From October 2016 to February 2017, I worked one day per week as an honorary public health registrar at Metro South Public Health Unit in Brisbane.

Summary of degree requirements

Investigate an acute public health event

While spending time as an honorary public health registrar at Metro South Public Health Unit in Brisbane, I investigated an outbreak of Q fever at an animal refuge and veterinary clinic in southeast Queensland (Chapter II). As part of this investigation, I interviewed cases and developed a self-administered questionnaire that was used to conduct a retrospective cohort study among workers at the animal refuge and veterinary clinic. We found that the outbreak was most likely due to exposure to an infected parturient cat that gave birth to a litter at the animal refuge, all of which were subsequently euthanised by veterinary clinic staff. As a result of our findings, we wrote a letter to the Australian Technical Advisory Group on Immunisation (ATAGI) recommending that occupational groups regularly exposed to parturient products of cats or dogs be recommended to receive Q fever vaccine and that this recommendation be included in the Australian Immunisation Handbook.

Establish a public health surveillance system

I established a surveillance system to identify newly acquired hepatitis C infections in Queensland (Chapter III). Prior to this project, Queensland was the only state not to identify or report newly acquired hepatitis C infections to the National Notifiable Diseases Surveillance System (NNDSS). The surveillance system I established uses data linkage to match new notifications of hepatitis C with previous negative anti-hepatitis C antibody test results. Following implementation of this system, Queensland now reports the highest number of newly acquired hepatitis C infections Australia-wide. In addition to the data linkage process, I implemented an enhanced surveillance pathway to collect information on reasons for testing and risk factors for hepatitis C virus (HCV) acquisition from diagnosing clinicians of newly acquired cases. I also developed and implemented criteria for further follow-up of cases without identified risk factors for HCV acquisition by the relevant PHUs.

Analyse a public health data set

The National Immunisation Program (NIP) currently funds a 3-dose primary course (3+0) of 13-valent pneumococcal conjugate vaccine at 2, 4, and 6 months of age. I performed descriptive analysis of vaccine breakthrough invasive pneumococcal disease (IPD) cases in Queensland following the introduction of pneumococcal conjugate vaccines (Chapter IV). I found that there has been an increase in the number of breakthrough IPD cases, the majority of which have been identified as serogroup 19A. Breakthrough cases of IPD occurred at a median age of 23 months, approximately 15 months after the final dose in the primary course, suggesting the potential benefit of a booster dose schedule. ATAGI has recently proposed a change to the pneumococcal vaccination schedule to include primary doses at 2 and 4 months of age, with a booster dose at 12 months.

Plan and conduct an epidemiological study

Individuals with medical conditions at elevated risk of invasive pneumococcal disease are recommended to receive pneumococcal vaccination in the Australian Immunisation Handbook. However, those with a previous episode of IPD are not included in the current Handbook recommendations, despite overseas evidence that they are at increased risk of future episodes. I planned and performed the analysis of a Queensland dataset of invasive pneumococcal disease notifications. to estimate the risk of recurrent IPD in Queensland (Chapter IV). This was achieved using time-to-event analysis and Cox Proportional Hazards modelling. We found that after an initial case of IPD, individuals experience future episodes at 35 times the rate of the general population. The risk of recurrence is even higher among Aboriginal and Torres Strait Islander people. As a result of our findings, we wrote to ATAGI recommending that a previous episode of IPD be included in the high-risk group of the Australian Immunisation Handbook, and be recommended to receive appropriate pneumococcal vaccination. We have recently received notice that this recommendation will be included in an updated version of the Pneumococcal disease chapter in the Handbook.

Prepare a scientific manuscript for a peer-reviewed journal

I prepared the following manuscript:

- An outbreak of Q fever associated with parturient cat exposure at an animal refuge and veterinary clinic in southeast Queensland (Chapter II), accepted for publication in the Australian and New Zealand Journal of Public Health

Communication to a lay audience

I wrote a one-page summary titled "Workplace Q Fever Outbreak Investigation Summary" to communicate the findings of the outbreak investigation to staff members of the workplaces where the outbreak occurred (Chapter II).

Conference presentations

I gave the following oral presentations at scientific conferences:

- Breakthrough cases of invasive pneumococcal disease in Queensland children following the introduction of pneumococcal conjugate vaccines, 2000–2015. Australian Epidemiological Association 23rd Annual Scientific Meeting, Canberra, Australia, 14–16 September 2016
- Estimating the risk of recurrent pneumococcal disease—Queensland, Australia, 2001–2015. 8th Southeast Asia and Western Pacific Bi-Regional TEPHINET conference, Siem Reap, Cambodia, 28 November–02 December 2016
- Estimating the risk of recurrent invasive pneumococcal disease in Queensland, 1997–2015. 15th World Congress on Public Health, Melbourne, Australia, 03–07 April 2017
- Using data linkage to identify newly acquired hepatitis C infections in Queensland. Communicable Diseases Control Conference 2017, Melbourne, Australia, 26-28 June 2017
- An outbreak of Q fever associated with domestic animal exposure at an animal refuge in southeast Queensland. Communicable Diseases Control Conference 2017, Melbourne, Australia, 26–28 June 2017

Lessons from the field

I prepared a teaching exercise titled "Tips and tricks for working with multiple records per subject in Stata" (Chapter V). I also attended Lessons from the Field exercises, prepared by fellow MAE scholars.

Teaching

I participated in the following teaching activities (Chapter V):

- Teaching during a session of the Outbreak Investigation subject for first-year MAE scholars
- Co-chairing a teaching session with fellow MAE scholar, Rose Wright, for the Issues in Applied Epidemiology subject, which focused on building social connection and trust among first-year MAE scholars

Coursework

I passed the following coursework subjects of the MAE Program:

- POPH8316—Outbreak Investigation
- POPH8317—Public Health Surveillance
- POPH8315—Research Design and Methods
- POPH8315—Analysis of Public Health Data
- POPH8914—Issues in Applied Epidemiology

Awards

I won the following awards for oral presentations related to my epidemiology study on estimating the risk of recurrent invasive pneumococcal disease in Queensland:

- Queensland regional Australasian Faculty of Public Health Medicine Gerry Murphy prize, 2016
- First prize, 8th Southeast Asia and Western Pacific Bi-Regional TEPHINET conference, Siem Reap, Cambodia, 2016

Additional field placement activities and other roles

In addition to activities related to the core requirements of the MAE Program, I also took part in the following projects and activities, and held additional roles during my placement (Chapter VI):

- Honorary public health registrar at Metro South Public Health Unit
- Weekly CDB notification meetings
- OzFoodNet Outbreak Control Team meetings and Multi-jurisdictional Outbreak Investigation teleconferences
- Expert Advisory Group member for a lookback investigation of a dental practice with infection control breaches
- An assessment of the need and suitability of rheumatic heart disease as a notifiable condition in Queensland; and
- World Health Organization Western Pacific Regional Office consultant epidemiologist for the "TB-Free Ebeye" project on the island of Ebeye, Republic of the Marshall Islands.

Summary of MAE requirements

A summary of my projects and activities, and how they meet the core MAE requirements, is provided in the table below.

Table—Summary of MAE projects and the fulfilment of core competencies and course requirements

	Chapter			
Degree requirements	**II**	**III**	**IV**	**V**
Outbreak investigation	■		■	
Establish a surveillance system		■	■	
Data analysis			■	
Epidemiological study			■	
Teaching activities				■
Conference presentation	■	■	■	
Communication with a lay audience	■			
Late draft of a peer review publication	■			

(This page left blank for aesthetic purposes)

II

Investigation of a Q fever outbreak at an animal refuge and veterinary clinic in southeast Queensland

Table of Contents

Prologue

This chapter describes the investigation of a Q fever outbreak at an animal refuge and veterinary clinic in southeast Queensland, from October to December 2016. The first case in the cluster was identified following the laboratory notification of Q fever in an animal refuge worker, who was hospitalised as a result of their infection in late-November 2016. Routine follow-up by Metro South Public Health Unit (MSPHU) revealed that additional animal refuge workers, and two staff members at an adjacent veterinary clinic, had reported having a non-specific febrile illness. An outbreak investigation was initiated after the second laboratory notification of Q fever in another animal refuge worker, one week after the first case was notified. The body of this chapter is the manuscript submitted to a scientific journal that summarises the outbreak investigation and its findings.

Project role

Commencing in late-October 2016, I spent one day a week at MSPHU as an honorary public health registrar to gain experience in the management and control of communicable diseases at an operational level. As part of this work, I led the epidemiological investigation of this outbreak and shared responsibilities with other public health unit staff for the initial interviewing of cases. I also followed up pathology results, gathered information from animal refuge and veterinary clinic management, and reviewed animal and euthanasia records. I developed a self-administered questionnaire to be completed by staff members in order to conduct a retrospective cohort study as part of the outbreak investigation (Appendix A), and entered and analysed the data. I wrote a one-page summary of the investigation findings to provide to the staff at the animal refuge and veterinary clinic (Appendix B) and have summarised the investigation findings in a manuscript which has been submitted to the Australian and New Zealand Journal of Public Health (accepted for publication).

Lessons learned

This was my first experience in leading an outbreak investigation and in developing a questionnaire for a study. Through interviewing cases and staff at the veterinary clinic, I was able to gain additional descriptive information that was useful in determining a plausible source of transmission. In developing, revising, and reviewing responses to the self-administered questionnaire, I gained valuable experience in the careful wording of questions to reduce the likelihood of misinterpretation by staff completing the questionnaire. In the design of the study, I collected information regarding the Q fever vaccination status of staff, allowing me to conduct a sensitivity analysis to avoid misclassification of asymptomatic cases and exclude those with pre-existing immunity. I felt this was a valuable practical learning point in study design and minimising potential sources of bias.

Public health impact

Q fever, caused by the intracellular bacterium *Coxiella Burnetii*, is a vaccine-preventable disease that can result in severe illness and long-term sequelae. Appropriate infection control practices and provision of Q fever vaccine are essential in reducing its burden among those at highest risk of disease. Traditionally, high-risk occupations include those where individuals are routinely exposed to cattle, sheep, and goats, such as abattoir workers. This investigation found that the outbreak was most likely due to a parturient cat that gave birth to a litter in an animal refuge, highlighting the risk of Q fever in non-livestock-related occupations.

Following notification of confirmed cases at the animal refuge and veterinary clinic, staff from Workplace Health & Safety Queensland (WHSQ) performed a site visit and reviewed infection control practices at the animal refuge centre. Animal refuge and veterinary clinic staff members subsequently underwent voluntary pre-vaccination screening and were offered Q fever vaccine if negative results were received to both screening tests.

A manuscript detailing this outbreak investigation has been accepted for publication in the Australian and New Zealand Journal of Public Health. The manuscript highlights the need for clinicians to be aware of exposure to parturient cats and dogs as a risk factor for Q fever, and recommends that occupational groups with regular exposure to parturient cats or dogs receive Q fever vaccine. I also wrote a letter to the Australian Technical Advisory Group on Immunisation (ATAGI) recommending that animal refuge workers be added to the list of recommended occupations to receive Q fever vaccine in the Q fever chapter of the *Australian Immunisation Handbook* (Appendix C).

Communication

- An outbreak of Q fever associated with domestic animal exposure at an animal refuge in southeast Queensland. Communicable Diseases Control Conference 2017, Melbourne, Australia, 26–28 June 2017
- Outbreak investigation summary provided to workplace (Appendix B)
- Letter to ATAGI (Appendix C)

MAE core activity requirements addressed

- Investigation of an acute public health event
- Peer-review publication
- Communication to a lay audience
- Presentation at a national conference

Acknowledgements

I acknowledge the contributions of MSPHU staff in the investigation of the outbreak, in particular, Kari Jarvinen for providing me with the opportunity to lead the epidemiological investigation and Candice Colbran and Deborah Judd for their assistance with multiple aspects of the investigation. I also thank OzFoodNet epidemiologists Russell Stafford and Robert Bell for lending their expertise in questionnaire development.

Abstract

Background: To determine the source of a human Q fever outbreak at an animal refuge and veterinary clinic in southeast Queensland from October to December 2016.

Methods: Case interviews and a retrospective cohort study of animal refuge and veterinary clinic staff using a self-administered questionnaire related to clinical history of Q fever, Q fever vaccination status, and workplace activities during the exposure period.

Results: Seven cases (six confirmed, one probable) were identified. Forty-three questionnaires were completed (91% response rate). Workplace activities associated with the greatest risk of illness were disposal of deceased cats or dogs (RR, 14.0; 95% CI, 1.9–104.1) and participating in euthanasia of cats or dogs (RR, 4.6; 95% CI, 1.3–16.9). Five feline birthing events occurred at the animal refuge from 25 September–19 October 2016, each with subsequent euthanasia of the queen cat and litter. All cases had likely exposure to a specific queen cat and her litter that were euthanised the same day as the birthing event.

Conclusions: A parturient cat was the most likely source of the outbreak. Occupational groups and others with regular exposure to feline or canine parturient products should receive Q fever vaccine.

Introduction

Q (query) fever is caused by the intracellular bacterium *Coxiella burnetii* and was first described among Queensland abattoir workers in 1937.[1] Transmission occurs through inhalation of *C. burnetii*-contaminated aerosols, usually generated from parturient products or slaughtering of infected animals.[2] As *C. burnetii* can survive in the environment for prolonged periods, infection can occur in those without direct animal contact.[2] The most commonly identified reservoirs are cattle, sheep, and goats.[2,3] Human outbreaks and cases are therefore generally reported in abattoir workers or those with livestock exposure,[1,2,4,5] though many cases have clear no risk factors for transmission identified.[5-7] In Australia, Q fever vaccine (Q-Vax, CSL Limited) is recommended for abattoir workers and other high-risk groups.[8] Q fever vaccine has demonstrated a signification reduction in the risk of developing Q fever in occupationally exposed populations, with a vaccine effectiveness of approximately 92% in a recent systematic review and meta-analysis.[9]

Serological evidence of *C. burnetii* infection has also been found in cats, dogs, kangaroos, flying foxes, bandicoots, and ticks.[2,4,10] Human outbreaks have been associated with exposure to both infected parturient cats[11-16] and dogs.[17] Australian estimates of *C. burnetii* seroprevalence range from 0–7.8% in cats[10,18] and 1.9–21.8% in dogs.[10,19,20] Despite moderate *C. burnetii* seropositivity in Australian feline and canine populations, reports of local human Q fever cases attributed to cat or dog exposures are exceedingly rare. The only documented feline-associated Q fever outbreak in Australia reported nine cases after a caesarean section was performed on an infected cat at a small animal veterinary clinic near Sydney in 2011.[15] A combination of the high proportion of asymptomatic Q fever infections[2] and low index of clinical suspicion in patients without a history of livestock exposure could lead to cat- and dog-related human Q fever being an unrecognised phenomenon in Australia.

On 17 November 2016, Metro South Public Health Unit (MSPHU) in Brisbane received laboratory notification of Q fever in an animal refuge worker. Routine

follow-up by MSPHU staff revealed that the case had been hospitalised and other animal refuge employees were experiencing non-specific febrile illnesses, including two staff members at an adjacent veterinary clinic. An outbreak investigation was initiated after laboratory confirmed infection in a second animal refuge worker. Our investigation focused on the most likely sources of infection—livestock, cats, and dogs.

Methods

Outbreak setting

The animal refuge had a livestock area that routinely kept sheep, goats, geese, ducks, and kangaroos. Dogs and cats were kept in separate impounds that were not accessible to the public. The veterinary clinic was adjacent (but not connected) to the animal refuge, and not in close proximity to the livestock area. Veterinary clinic staff regularly attended the animal refuge to perform euthanasia of cats and dogs.

Case definitions and exposure period

Confirmed and probable case definitions were developed (Box). The incubation period for *C. burnetii* (4 days[14] to 6 weeks) was used to define a likely common exposure period for cases.[2]

Case-finding

Animal refuge and veterinary clinic staff who were unwell prior to or during the investigation were encouraged to contact MSPHU and request their usual medical practitioner perform testing for Q fever. All cases of Q fever notified to MSPHU during the outbreak investigation (who were not employees of the animal refuge or veterinary clinic) were asked if they had visited an animal refuge in southeast Queensland during their exposure period. Neighbouring public health units were alerted to the outbreak and requested to also determine if new Q fever cases had visited an animal refuge.

Box—Case definitions used during a Q fever outbreak at an animal refuge and veterinary clinic in southeast Queensland, 2016

Confirmed case
From 15 September to 31 December 2016, any animal refuge or veterinary clinic staff with either: 1. Detection of *C. burnetii* through nucleic acid testing OR 2. Presence of IgM antibodies to *C. burnetii* AND a clinically compatible illness.
Probable case
From 15 September to 31 December 2016, any animal refuge or veterinary clinic staff with: 1. A clinically compatible illness (e.g. fever, influenza-like illness, pneumonia, hepatitis) AND 2. No previous clinical history of Q fever AND 3. No previous record of receiving Q fever vaccine.

Case interviews

All confirmed and probable cases were interviewed using the standard Queensland Health Q fever Case Report Form[21] and dates of work were ascertained for the common exposure period.

Animal records

Records of livestock present at the animal refuge from mid-September until the onset date of the earliest case were reviewed. Euthanasia records for cats, kittens, and dogs at the animal refuge for the same time period were also examined to explore the potential likelihood of transmission events. Euthanasia records included dates of birth for kittens born at the animal refuge and veterinary staff who performed the euthanasia.

Site visit

MSPHU staff alerted Workplace Health and Safety Queensland (WHSQ) of the outbreak. WHSQ subsequently performed a site visit of the animal refuge in late-November 2016.

Employees of the animal refuge and veterinary clinic were offered Q fever pre-vaccination screening (intradermal hypersensitivity test and serum

complement-fixation antibody test). Q fever vaccine was offered to those with negative results to both screening tests.

Self-administered questionnaire

We conducted a retrospective cohort study among animal refuge and veterinary clinic staff to determine workplace activities associated with Q fever infection. A paper-based, self-administered questionnaire with questions related to clinical history of Q fever, Q fever vaccination status, and workplace activities from 15 September to 31 October 2016 was developed. The questionnaire was delivered to animal refuge and veterinary clinic management for distribution among staff members (including cases) and was collected one week later. Due to the non-specific nature of clinical Q fever and the high proportion of asymptomatic infections, questions related to symptoms were not included in the questionnaire to assist with case finding.

Data analysis

Individuals who reported receiving Q fever vaccine more than six weeks prior to the onset of the first case were deemed to be at low risk of infection[9] and were excluded from analysis. Risk ratios were calculated, comparing cases and non-cases, for visiting the livestock area, cat impound, dog impound, and for specific workplace activities within these areas. Individuals who reported not visiting the livestock area, cat impound, or dog impound were excluded from further analysis of workplace activities specific to that area. Fisher's exact p-values were calculated for corresponding risk ratios, with $p<0.05$ considered significant. For exposures with a risk ratio of infinity, exact logistic regression was used to calculate an odds ratio and the lower bound of the 95% confidence interval.

Individuals who underwent Q fever pre-vaccination screening after the investigation commenced, and reported receiving the vaccine negative screening results, were classified as susceptible non-cases. To control for the potential misclassification of asymptomatic cases or inclusion of individuals with pre-existing immunity, a sensitivity analysis was performed comparing exposures of

cases to susceptible non-cases. All analyses were performed using Stata 14.1 (Stata Corp, USA).

Ethics approval

This investigation was carried out under the powers in the Queensland *Public Health Act 2005* in response to an acute threat to public health in order to determine the likely source of disease transmission and potential ongoing risk to staff and the public. Ethics approval was therefore not required.

Results

Cases

Seven cases (six confirmed, one probable) were identified among 47 staff members (15% attack rate), with illness onset dates from 21 October to 20 November 2016 (Figure 1). Two confirmed cases had *C. burnetii* detected through nucleic acid testing. The probable case had a non-specific febrile illness with elevated inflammatory markers, elevated liver enzymes, no previous clinical history of Q fever, and no record of receiving Q fever vaccine. Confirmatory testing was unable to be performed for the probable case. Two (29%) cases were hospitalised as a result of their illness (Case 1, for five days; Case 4, for two days). The common exposure period was from 09 to 17 October (Figure 2). No visits to an animal refuge were reported among notified cases of Q fever in southeast Queensland (who were not animal refuge or veterinary clinic staff) during the investigation.

Case interviews

Five cases (83%) were animal refuge workers with varying roles including management, cleaning of animal areas, and disposal of deceased animals after euthanasia. Case 1 handled cats and kittens during euthanasia and also attended to laundry at the veterinary clinic. Multiple staff reported that personal protective equipment (PPE) was not routinely used in the handling of animals or newborn kittens during euthanasia.

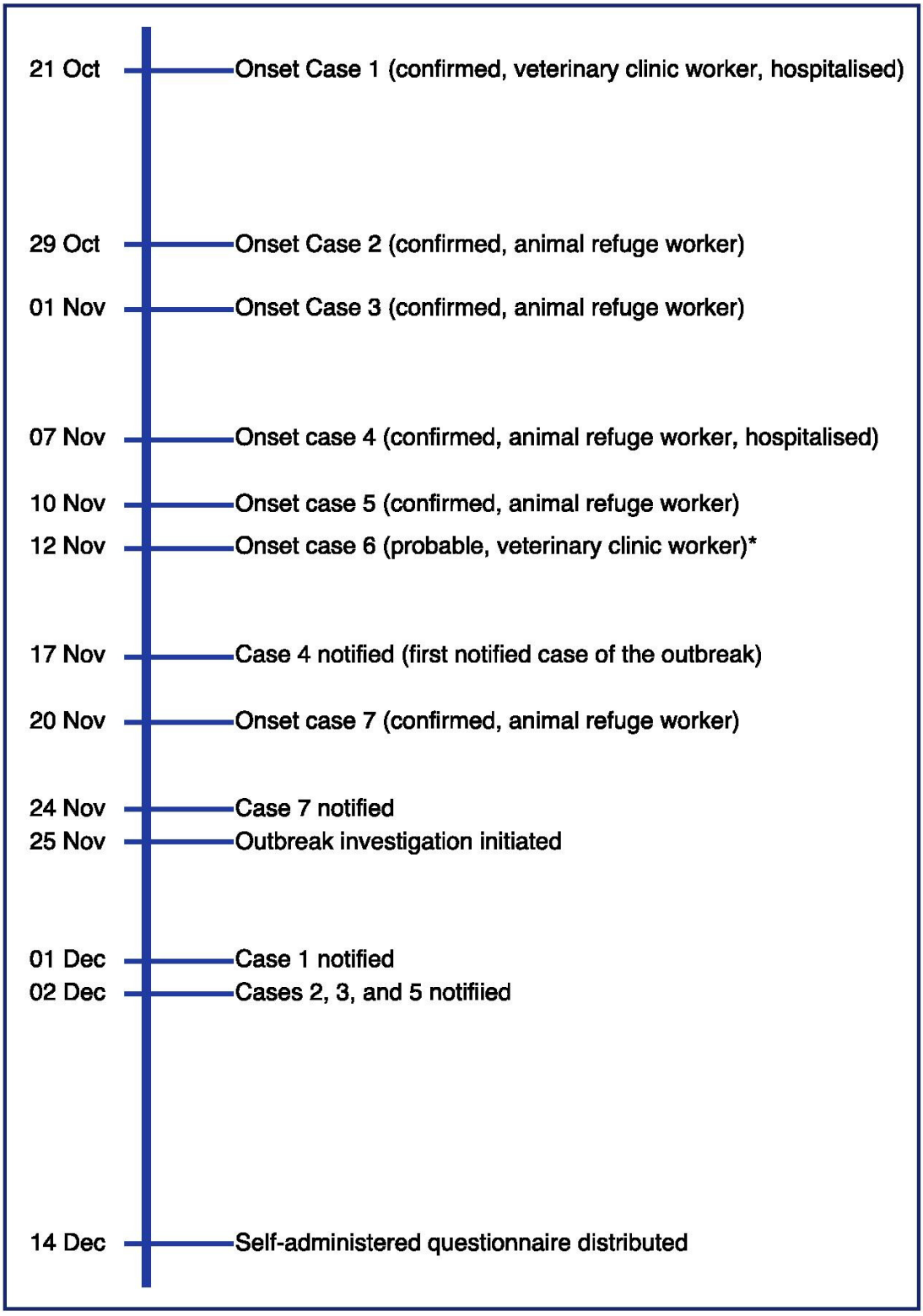


Figure 1— Timeline of Q fever outbreak at an animal refuge and veterinary clinic in southeast Queensland, 2016. *The probable case (case 6) was not notified and came to attention through follow-up of other notified cases.

Animal records

Veterinary clinic staff attended the livestock area in mid-September to review an unwell, 3-month-old goat. The goat was kept at the animal refuge for less than one week before being transferred for adoption and was unavailable for Q fever testing. No livestock births occurred during the common exposure period and livestock slaughtering did not occur at the animal refuge.

From 25 September to 19 October, there were records of five feline birthing events at the cat impound where the queen cats and their litters were eventually euthanised by veterinary clinic staff. A birthing event on 07 October—when all cases were present at work—involved a cat that had been caught in a trap by the local council on 05 October. This cat delivered her litter prematurely and they were all subsequently handled and euthanised the same day. As a common exposure, this event equates to maximum incubation periods of 14 and 44 days for Cases 1 and 7, respectively. The four other occasions where a queen cat and her litter were euthanised occurred on days when either all cases were not present at work, euthanasia was not performed on the same day as the birthing event, euthanasia was performed by a susceptible non-case, or the corresponding incubation periods fell outside the known range. The origin of these four queen cats was not ascertained during the investigation. There were no reports of euthanised puppies in the records reviewed. Animal cadavers were collected and disposed of on a weekly basis and were therefore unavailable for testing.

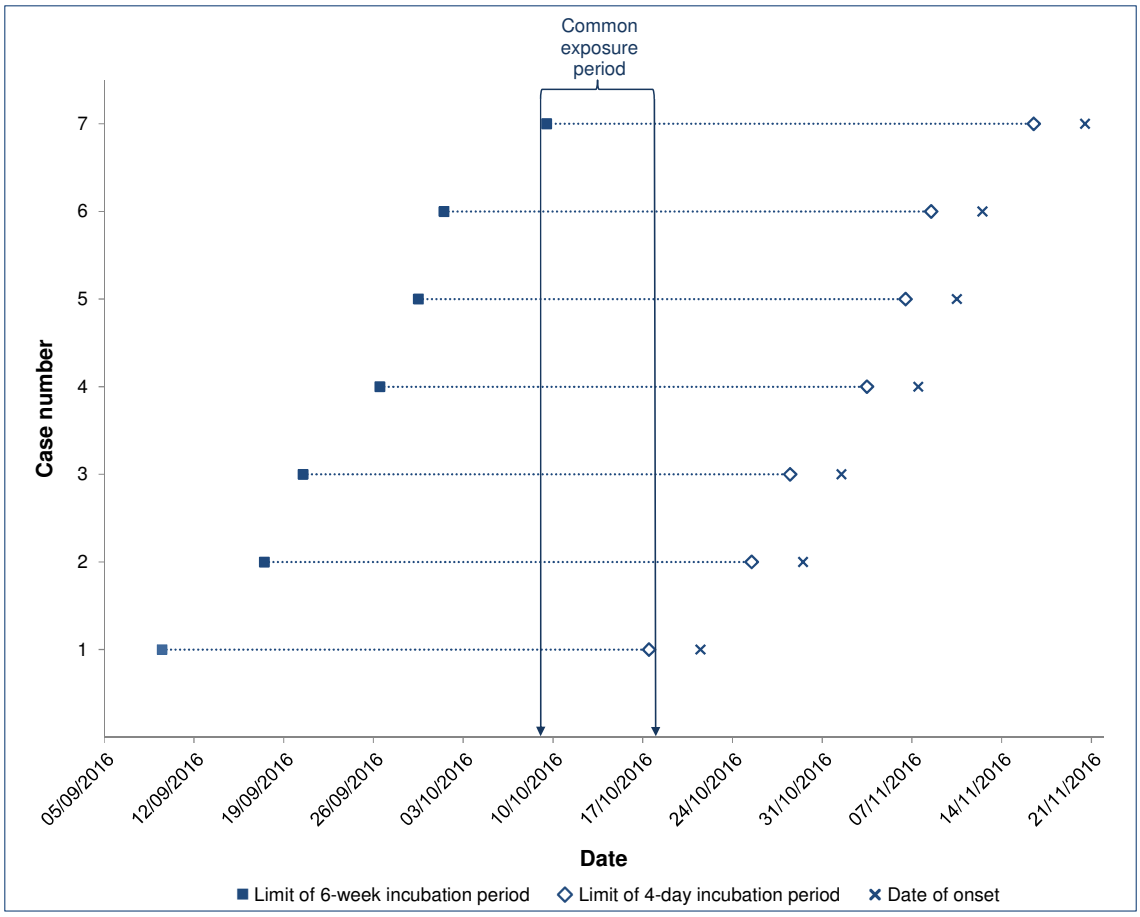


Figure 2—Exposure periods for cases of Q fever (confirmed and probable) during an outbreak at an animal refuge and veterinary clinic in southeast Queensland, 2016

Self-administered questionnaire

Forty-three (91% response rate) questionnaires were completed by workers (both cases and non-cases) at the animal refuge (38) and veterinary clinic (5). Three animal refuge workers reported receiving Q fever vaccine more than 6 weeks prior to the onset date of Case 1 and were excluded from the analysis. All cases reported attending each of the livestock area, cat impound, and dog impound between 15 September and 31 October.

Activities associated with the greatest risk of illness were disposal of deceased dogs or puppies, disposal of deceased cats or kittens, providing or assisting with euthanasia of dogs, and providing or assisting with euthanasia of cats or kittens (Table). After aggregating dog- and cat-related activities, disposal of deceased animals (RR, 14.0; 95% CI, 1.9–104.1, p=0.001) and providing or assisting with

the euthanasia of animals (RR, 4.6; 95% CI, 1.3–16.9, p=0.03) remained the activities associated with highest risk of illness.

Twenty individuals reported receiving Q fever vaccine after commencement of the investigation. The sensitivity analysis, including only susceptible non-cases (n=20) and all cases, demonstrated a similar pattern of risk ratios reported in the Table (Appendix D). However, the exposures with the highest associated risk, disposal of deceased dogs or puppies (RR, 4.2; 95% CI, 1.0–17.2, p=0.06) and disposal of deceased cats or kittens (RR, 3.6; 95% CI, 0.9–14.6, p=0.07), were no longer statistically significant.

Table—Attack rates and risk ratios for workplace-related exposures of Q fever cases (confirmed and probable) and non-cases during an outbreak at an animal refuge and veterinary clinic in southeast Queensland, 2016*

	Exposed			Unexposed					
	Total	Cases	AR (%)	Total	Cases	AR (%)	RR	95% CI	p-value†
Livestock area									
Visit to livestock area	29	7	24.1	11	0	0	4.4‡	0.6–∞	0.16
Contact with any livestock (sheep, goat, horses, poultry)	25	6	24.0	4	1	25	1	0.2–6.0	1
Cleaning of livestock area or animal pens	10	2	20.0	19	5	26.3	0.8	0.2–3.2	1
Cat impound									
Visit to cat impound	31	7	22.6	9	0	0	3.3‡	0.4–∞	0.18
Direct contact with cats or kittens	28	7	25.0	3	0	0	1.2‡	0.1–∞	1
Handling cats/kittens at birth, or present during birthing events	13	4	30.8	18	3	16.7	1.8	0.5–6.9	0.41
Providing or assisting with euthanasia of cats or kittens	9	4	44.4	22	3	13.6	3.3	0.9–11.7	0.15
Disposal of deceased cats or kittens	11	5	45.5	20	2	10	4.5	1.1–19.7	0.07
Cleaning of cat impound, cages or changing cat litter	12	3	25.0	19	4	21.1	1.2	0.3–4.4	1
Dog impound									
Visit to dog impound	34	7	20.6	6	0	0	1.0‡	0.2–∞	0.57
Direct contact with dogs or puppies	32	6	18.8	2	1	50	0.4	0.1–1.8	0.37
Handling dogs/puppies at birth, or present during birthing events	6	1	16.7	28	6	21.4	0.8	0.1–5.3	1
Providing or assisting with euthanasia of dogs	8	4	50.0	26	3	11.5	4.3	1.2–15.4	0.04
Disposal of deceased dogs or puppies	9	5	55.6	25	2	8	6.9	1.6–29.7	0.007
Cleaning of dog impound, cages or dog waste	14	3	21.4	20	4	20	1.1	0.3–4.1	1

*The outbreak occurred from October–December 2016 and the workplace-related exposures were reported from 15 September–31 October 2016. †Fisher's exact p-value. ‡Odds ratio and lower bound of the 95% confidence interval calculated using exact logistic regression. AR, attack rate; RR, risk ratio.

Discussion

We found descriptive and epidemiological evidence that this outbreak of Q fever was likely caused by exposure to parturient products of an infected cat. The most plausible source was the queen cat that delivered her litter prematurely on 07 October, all of which were subsequently euthanised the same day. *C. burnetii* has been detected in cats having an abortion or delivering stillbirths, and associated with prematurity and abortion in other animals.[22] If this was a point-source outbreak, the range of incubation periods was 14–44 days. The upper limit of this range is similar to the previously reported extreme,[23] although environmental contamination with delayed transmission is also possible. Case 1, with the earliest onset of illness, was likely to have had the highest exposure dose to infectious material through assisting with euthanasia of cats and attending to laundry at the veterinary clinic—consistent with the dose-dependent incubation period of acute Q fever infection[1,24] and known transmission routes.[12]

The origin of the implicated queen cat (from a council trap) is of potential interest, as feline subpopulations are likely to differ in their potential for acquiring *C. burnetii* infection. Of two previous Australian *C. burnetii* seroprevalence studies, one found the highest seropositivity among cattery-confined cats, with zero seropositivity in feral and shelter cats,[18] while the other examined urine samples from domesticated cats at a veterinary surgery.[10] The seroprevalence of *C. burnetii* among shelter and feral cats in Australia is therefore unknown, and requires further investigation to determine the risk of human Q fever infection from this source.

While six of the seven cases reported having direct contact with livestock, the absence of livestock birthing events, slaughtering, and corresponding risk ratios for livestock-related activities makes this an unlikely source of disease transmission. Disposal of deceased dogs or puppies and assisting with the euthanasia of dogs were associated with an increased risk of illness. However, only one case reported exposure to dogs giving birth during the exposure period, making this an unlikely mode of infection. For most cases, cat- and dog-related

activities were correlated, providing an explanation for the significant association with some dog-related activities in the absence of a high-risk exposure event for Q fever in the dog impound. The lack of other plausible sources of transmission supports our conclusion that this outbreak was due to an infected parturient cat.

Outbreaks of Q fever associated with parturient cats have been reported in the United States,[13] Canada,[11,12,16] and Australia.[15] Our outbreak was detected following the hospitalisation, Q fever testing, and subsequent laboratory notification of two cases. This outbreak likely would have gone undetected had these two cases developed a milder clinical illness not requiring hospitalisation. A history of exposure to parturient domestic animals should serve as an indication for Q fever testing in patients with an unexplained, non-specific febrile illness.

Q fever vaccination for all veterinarians, veterinary nurses, and veterinary students, and the use of PPE during exposure to parturient products was recommended in the first (2011)[25] and two subsequent (2013, 2017)[26,27] editions of the Australian Veterinary Association *Guidelines for Veterinary Personal Biosecurity*. Surprisingly, none of the veterinary clinic staff and only three animal refuge workers had previously received Q fever vaccine. Additionally, PPE was not reported as being used by animal refuge or veterinary clinic workers involved with euthanasia, even when exposed to parturient products. These practices are consistent with previous reports demonstrating a relatively low perceived risk of Q fever among Australian veterinary workers[28] and cat breeders.[29] Additionally, *The Australian Immunisation Handbook* recommends Q fever vaccine for professional dog and cat breeders,[8] though other occupations with exposure to parturient cats and dogs are not currently included in this recommendation. Given our finding that feline birthing events were a relatively common occurrence in the cat impound, workers in these settings are likely to experience a similar exposure risk to that of professional dog and cat breeders. Animal refuge workers and others with regular exposure to parturient cats or dogs should therefore also be included in the recommendation to receive Q fever vaccine after undergoing pre-vaccination

screening. Ongoing communication from Workplace Health and Safety, State Departments of Health, and the Australian Veterinary Association regarding the risk of Q fever infection—reinforcing the use of PPE and Q fever vaccination—should be provided to those in the veterinary and non-veterinary workforces with routine exposure to parturient cats or dogs. Promoting the use of PPE as part of routine infection control practices in veterinary and non-veterinary workforces is also of importance, given the potential for infection with other zoonoses.

Our investigation was limited by the lack of Q fever serological testing for all workers at the animal refuge and veterinary clinic, resulting in potentially misclassifying asymptomatic cases and including non-cases with pre-existing immunity. We also did not include questions related to symptoms of Q fever in the self-administered questionnaire, which may have assisted in identifying additional cases that would benefit from Q fever serology. There is potential for differential misclassification of unidentified cases as non-ill in the primary analysis of the cohort. However, sensitivity analyses, including only the cohort who underwent Q fever pre-vaccination screening and subsequently received Q fever vaccination as susceptible non-cases, revealed a similar pattern of risk ratios for workplace exposures when compared to the primary analysis. As this investigation was undertaken as part of an acute public health response in a busy metropolitan public health unit, a more comprehensive approach involving serum sampling of all at-risk staff was not feasible.

We were also limited by the inability to test for markers of *C. burnetii* infection in the implicated cat, as was performed during the previous Australian cat-related outbreak.[15] This testing would have provided additional evidence to either support or refute our conclusions.

Conclusions

Our outbreak investigation highlights that parturient cats and dogs are potentially unrecognised sources of sporadic Q fever cases and outbreaks in Australia. A history of exposure to feline or canine parturient products should increase clinical suspicion for Q fever in patients with an unexplained, non-specific febrile illness. Q fever vaccine should be provided to susceptible individuals with occupational or other regular exposure to parturient cats or dogs.

References

1. Derrick E. "Q" fever, a new fever entity: clinical features, diagnosis and laboratory investigation. *Med J Aust* 1937;2(8):281-99.

2. Maurin M, Raoult D. Q fever. *Clin Microbiol Rev* 1999;12(4):518-53.

3. Eldin C, Mélenotte C, Mediannikov O, Ghigo E, Million M, Edouard S, et al. From Q fever to *Coxiella burnetii* infection: a paradigm change. *Clin Microbiol Rev* 2017;30(1):115-90.

4. Parker NR, Barralet JH, Bell AM. Q fever. *Lancet* 2006;367(9511):679-88.

5. Sloan-Gardner TS, Massey PD, Hutchinson P, Knope K, Fearnley E. Trends and risk factors for human Q fever in Australia, 1991–2014. *Epidemiol Infect* 2016;145(4):787-95.

6. Chong A, Brooy JL, Norton R, Masson J. Q fever: a recent 'outbreak'in Townsville. *Intern Med J* 2003;33(4):208-10.

7. Archer BN, Hallahan C, Stanley P, Seward K, Lesjak M, Hope K, et al. Atypical outbreak of Q fever affecting low-risk residents of a remote rural town in New South Wales. *Commun Dis Intell Q Rep* 2017;41(2):E125-33.

8. Australian Technical Advisory Group on Immunisation. *The Australian immunisation handbook (10th ed): 4.15 Q fever* [Internet]. Canberra (AUST): Australian Government Department of Health; 2017 [cited 2017 Sept 1]. Available from: http://www.immunise.health.gov.au/internet/immunise/publishing.nsf/Content/Handbook10-home~handbook10part4~handbook10-4-15

9. O'Neill T, Sargeant J, Poljak Z. The effectiveness of *Coxiella burnetii* vaccines in occupationally exposed populations: a systematic review and meta-analysis. *Zoonoses Public Health* 2014;61(2):81-96.

10. Tozer S, Lambert S, Strong C, Field H, Sloots T, Nissen M. Potential animal and environmental sources of Q fever infection for humans in Queensland. *Zoonoses Public Health* 2014;61(2):105-12.

11. Kosatsky T. Household outbreak of Q-fever pneumonia related to a parturient cat. *Lancet* 1984;324(8417):1447-9.

12. Marrie TJ, Langille D, Papukna V, Yates L. Truckin' pneumonia—an outbreak of Q fever in a truck repair plant probably due to aerosols from clothing contaminated by contact with newborn kittens. *Epidemiol Infect* 1989;102(1):119-27.

13. Pinsky RL, Fishbein DB, Greene CR, Gensheimer KF. An outbreak of cat-associated Q fever in the United States. *J Infect Dis* 1991;164(1):202-4.

14. Marrie TJ, Durant H, Williams JC, Mintz E, Waag DM. Exposure to parturient cats: a risk factor for acquisition of Q fever in Maritime Canada. *J Infect Dis* 1988;158(1):101-8.

15. Kopecny L, Bosward KL, Shapiro A, Norris JM. Investigating *Coxiella burnetii* infection in a breeding cattery at the centre of a Q fever outbreak. *J Feline Med Surg* 2013;15(12):1037-45.

16. Langley JM, Marrie TJ, Covert A, Waag DM, Williams JC. Poker players' pneumonia: an urban outbreak of Q fever following exposure to a parturient cat. *N Engl J Med* 1988;319(6):354-6.

17. Buhariwalla F, Cann B, Marrie T. A dog-related outbreak of Q fever. *Clin Infect Dis* 1996;23(4):753-5.

18. Shapiro AJ, Bosward KL, Heller J, Norris JM. Seroprevalence of *Coxiella burnetii* in domesticated and feral cats in eastern Australia. *Vet Microbiol* 2015;177(1–2):154-61.

19. Cooper A, Hedlefs R, Ketheesan N, Govan B. Serological evidence of *Coxiella burnetii* infection in dogs in a regional centre. *Aust Vet J* 2011;89(10):385-7.

20. Shapiro A, Norris J, Heller J, Brown G, Malik R, Bosward K. Seroprevalence of *Coxiella burnetii* in Australian dogs. *Zoonoses Public Health* 2016;63(6):458-66.

21. Queensland Health. *Q Fever Case Report Form* [Internet]. Brisbane (AUST): Queensland Government; 2011 [cited 2017 Sept 1]. Available from: http://disease-control.health.qld.gov.au/Condition/749/q-fever

22. Agerholm JS. *Coxiella burnetii* associated reproductive disorders in domestic animals: a critical review. *Acta Vet Scand* 2013;55(1):13.

23. Raoult D, Thomas M. Q Fever. *Clin Infect Dis* 1995;20(3):489-95.

24. Tigertt WD, Benenson AS, Gochenour WS. Airborne Q fever. *Bacteriol Rev* 1961;25(3):285-93.

25. Australian Veterinary Association. *Guidelines for veterinary personal biosecurity version 1.0*. St Leonards (AUST): Australian Veterinary Association; 2011.

26. Australian Veterinary Association. *Guidelines for veterinary personal biosecurity (2nd ed)*. St Leonards (AUST): Australian Veterinary Association; 2013.

27. Australian Veterinary Association. *Guidelines for veterinary personal biosecurity (3rd ed)*. St Leonards (AUST): Australian Veterinary Association; 2017.

28. Sellens E, Norris JM, Dhand NK, Heller J, Hayes L, Gidding HF, et al. Q fever knowledge, attitudes and vaccination status of Australia's veterinary workforce in 2014. *PLoS One* 2016;11(1):e0146819.

29. Shapiro A, Norris J, Bosward K, Heller J. Q fever (*Coxiella burnetii*) knowledge and attitudes of Australian cat breeders and their husbandry practices. *Zoonoses Public Health* 2017;64(4):252-61.

Appendix A—Work-related activities questionnaire

Work-Related Activities Questionnaire

Queensland Government

Metro South Health

Metro South Public Health Unit

PRIVACY MESSAGE

The information you provide in this questionnaire is for the purpose of trying to prevent further cases of illness.
The data collected in this questionnaire is kept confidential.

We are investigating cases of illness at your workplace and are interested in your work-related activities from September 15th to October 31st 2016.

To assist us in our investigation, please complete every question to the best of your ability.

Details of person completing the questionnaire *(this information is kept confidential)*		
First Name:	Last Name:	
DOB: ____/____/____ Age:	Gender: ☐M ☐F	
Mobile Phone:	Work Phone:	Postcode:

Q1. At which of the following sites are you usually employed? *(i.e. not including other places of employment)*

☐Logan City Council Animal Management Centre ☐Combined Vets Kingston

Q2. History of vaccination, testing, and treatment for Q Fever	
2a) Have you *ever* been given a vaccination for Q Fever:	☐Yes ☐No ☐Unsure
2b) *In the past 3 months,* have you been given a vaccination for Q Fever:	☐Yes ☐No ☐Unsure
2c) Have you *ever* had a positive blood or skin test for Q Fever:	☐Yes ☐No ☐Unsure
2d) *In the past 3 months*, have you had a positive blood or skin test for Q Fever:	☐Yes ☐No ☐Unsure
2e) Have you *ever* been diagnosed with Q Fever:	☐Yes ☐No ☐Unsure
2f) *In the past 3 months*, have you been diagnosed with Q Fever:	☐Yes ☐No ☐Unsure

Q3. Activities in the **pen/livestock area** at Logan City Council Animal Management Centre from Sept 15th–Oct 31st 2016		
3a) From Sept 15th–Oct 31st 2016, did you visit/work in the **pen/livestock area** where goats and sheep are kept? ☐Yes ☐No *(If no, proceed to Question 4)*		
3b) From Sept 15th–Oct 31st 2016, on average, how frequently did you visit/work in the **pen/livestock area**? ☐4 or more times per week ☐2-3 times per week ☐Once per week ☐Once per fortnight ☐Once per month		
3c) From Sept 15th–Oct 31st 2016, when you visited/worked in the **pen/livestock area**, were you involved in any of the following activities?		
i.	Direct contact with sheep (touching, petting, grooming):	☐Yes ☐No ☐Unsure
ii.	Direct contact with goats (touching, petting, grooming):	☐Yes ☐No ☐Unsure
iii.	Direct contact with other livestock: *If yes, please specify animal type(s):*_____	☐Yes ☐No ☐Unsure
iv.	Present during or assisting with the birth of livestock: *If yes, please specify animal type(s):*_____	☐Yes ☐No ☐Unsure
v.	Handling of newborn livestock, immediately after or during birth: *If yes, please specify animal type(s):*_____	☐Yes ☐No ☐Unsure
vi.	General cleaning of pen/livestock area:	☐Yes ☐No ☐Unsure
vii.	Cleaning of animal pens:	☐Yes ☐No ☐Unsure

CONTINUED ON OTHER SIDE

Q4. Activities in the **cat impound** at Logan City Council Animal Management Centre from Sept 15th–Oct 31st 2016				
4a) From Sept 15th–Oct 31st 2016, did you visit/work in the **cat impound**? ☐Yes ☐No *(If no, proceed to Question 5)*				
4b) From Sept 15th–Oct 31st 2016, on average, how frequently did you visit/work in the **cat impound**? ☐4 or more times per week ☐2-3 times per week ☐Once per week ☐Once per fortnight ☐Once per month				
4c) From Sept 15th–Oct 31st 2016, when you visited/worked in the **cat impound**, were you involved in any of the following activities?				
	i.	Direct contact with newborn kittens (touching, petting, grooming):	☐Yes ☐No	☐Unsure
	ii.	Direct contact with cats, excluding kittens (touching, petting, grooming):	☐Yes ☐No	☐Unsure
	iii.	Handling female cats during or immediately after giving birth:	☐Yes ☐No	☐Unsure
	iv.	Handling kittens during or immediately after birth:	☐Yes ☐No	☐Unsure
	v.	Present in the cat impound while cats were giving birth:	☐Yes ☐No	☐Unsure
	vi.	Assisting with or providing euthanasia to newborn kittens:	☐Yes ☐No	☐Unsure
	vii.	Assisting with or providing euthanasia to cats, excluding kittens:	☐Yes ☐No	☐Unsure
	viii.	Disposal of deceased cats or kittens:	☐Yes ☐No	☐Unsure
	ix.	General cleaning of the cat impound:	☐Yes ☐No	☐Unsure
	x.	Cleaning of cat cages:	☐Yes ☐No	☐Unsure
	xi.	Changing or disposing of cat litter:	☐Yes ☐No	☐Unsure

Q5. Activities in the **dog impound** at Logan City Council Animal Management Centre from Sept 15th–Oct 31st 2016				
5a) From Sept 15th–Oct 31st 2016, did you visit or work in the **dog impound**? ☐Yes ☐No *(If no, questionnaire completed)*				
5b) From Sept 15th–Oct 31st 2016, on average, how frequently did you visit/work in the **dog impound**? ☐4 or more times per week ☐2-3 times per week ☐Once per week ☐Once per fortnight ☐Once per month				
5c) From Sept 15th–Oct 31st 2016, when you visited/worked in the **dog impound**, were you involved in any of the following activities?				
	i.	Direct contact with newborn puppies (touching, petting, grooming):	☐Yes ☐No	☐Unsure
	ii.	Direct contact with dogs, excluding puppies (touching, petting, grooming):	☐Yes ☐No	☐Unsure
	iii.	Handling female dogs during or immediately after giving birth:	☐Yes ☐No	☐Unsure
	iv.	Handling puppies during or immediately after birth:	☐Yes ☐No	☐Unsure
	v.	Present in the dog impound while dogs were giving birth:	☐Yes ☐No	☐Unsure
	vi.	Assisting with or providing euthanasia to newborn puppies:	☐Yes ☐No	☐Unsure
	vii.	Assisting with or providing euthanasia to dogs, excluding puppies:	☐Yes ☐No	☐Unsure
	viii.	Disposal of deceased dogs or puppies:	☐Yes ☐No	☐Unsure
	ix.	General cleaning of the dog impound:	☐Yes ☐No	☐Unsure
	x.	Cleaning of dog cages:	☐Yes ☐No	☐Unsure
	xi.	Changing or disposing of waste from dog cages:	☐Yes ☐No	☐Unsure

Can Metro South Public Health Unit contact you if further information is required? ☐Yes ☐No

END QUESTIONNAIRE

PLEASE INSERT INTO PROVIDED ENVELOPE AND RETURN TO YOUR MANAGER

Appendix B—Outbreak investigation summary

Queensland Government

Metro South Health
Metro South Public Health Unit

Workplace Q Fever Outbreak
Investigation Summary

7th February 2017

Thank you for your cooperation in our investigation of a Q fever outbreak at your workplace from October to December 2016. We have summarised the findings of our investigation for your information.

Q Fever

Q fever is caused by the bacteria *Coxiella burnetii*. Humans usually become infected through contact with cattle, sheep and goats, although kangaroos, cats, dogs and other animals can also carry the bacteria and cause human infection.

Infected animals spread the bacteria through urine, faeces, milk and birthing products. After coming into contact with the bacteria, humans usually take 2 to 3 weeks to become unwell, but only half of the people who become infected will show symptoms of illness.

Outbreak Investigation

Our investigation focused on the most likely sources of infection in your workplace—livestock (sheep and goats) and cats or dogs giving birth in the impound.

Samples from animals or the workplace could not be taken to test for Q fever. We therefore relied on discussions with staff, reviewing animal and euthanasia records, and a workplace activities questionnaire to determine the most likely sources of infection.

Investigation Findings

After reviewing animal and euthanasia records, possible sources of infection included a young, unwell goat and two queen cats that either gave birth or aborted kittens that were euthanised shortly afterwards.

Responses to the workplace activities questionnaire showed that those who provided or assisted with euthanising cats or dogs and those involved with the disposal of deceased cats or dogs were more likely to become unwell with Q fever.

Summary

While a definitive source of infection was unable to be determined through our investigation, our findings suggest the most likely source was the birthing products of an infected queen cat.

People who have been vaccinated against Q fever, or been infected with Q fever, have high levels of protection against future illness.

Thank you again for your assistance with our investigation.

Regards,

Dr Kari Jarvinen
A/Director and Public Health Physician
Metro South Public Health Unit

Appendix C—Letter to ATAGI

ATAGI Secretariat
Department of Health
Immunisation Branch
GPO Box 9848 - MDP 13
CANBERRA ACT 2601

ATAGI.Secretariat@health.gov.au

20 March 2017

Dear ATAGI Secretariat

Re: Animal refuge workers as an at-risk occupation for Q fever

We are writing with regards to the list of occupations recommended to receive Q fever vaccine in the Q fever chapter of the Australian Immunisation Handbook.

We have recently investigated a Q fever outbreak at an animal refuge in southeast Queensland. Our findings highlight that animal refuge workers are at risk of occupationally acquired Q fever infection and should be a specific at-risk group recommended to receive Q fever vaccine.

In addition to occupations routinely exposed to livestock (abattoir workers, farmers, shearers etc.), the Handbook also recommends Q fever vaccine for veterinarians, veterinary nurses, veterinary students, professional dog and cat breeders, agricultural college staff and students, wildlife and zoo workers, and laboratory personnel handling veterinary specimens or working with *Coxiella burnetii*.

Animal refuge workers have the potential for routine exposure to *C. burnetii* aerosols through infected domestic (cats and dogs) animals that give birth at animal refuges. This is the identical risk exposure faced by professional dog and cat breeders, for whom vaccination is currently recommended. An outbreak at a veterinary clinic in Sydney in 2010 caused by an infected queen cat highlights the potential for human Q

fever cases arising from exposure to infected domestic animals, a risk that is further supported by our investigation.

In November 2016, an outbreak investigation was initiated by Metro South Public Health Unit (MSPHU) after two laboratory notifications of Q fever were received one week apart. One was in an animal refuge worker and one in a veterinary nurse at a veterinary clinic adjacent to the animal refuge—both of whom had been hospitalised due to their infection. Routine follow-up of these two notifications revealed that five additional staff members had a non-specific febrile illness in the same time period.

We conducted a cohort study using a self-administered, paper-based questionnaire, of animal refuge and veterinary clinic staff to determine what workplace activities were associated with an increased risk of illness. The questionnaire included questions related to clinical history of Q fever, Q fever vaccination status, and workplace-related activities during the exposure period.

There were seven (six confirmed and one probable) Q fever cases identified (Figure). The one probable case (veterinarian) had a clinically compatible illness with rising IgG titres, no previous history of Q fever vaccination or diagnosis, and an absent IgM antibody response. Other cases included those involved with management, cleaning, and disposal of deceased animal cadavers at the animal refuge, and one veterinary clinic nurse.

For the cohort study, 43 (92% response rate) questionnaires were completed by workers at the animal refuge centre (38) and veterinary clinic (5). Three animal refuge workers and no veterinary clinic staff reported previously receiving Q fever vaccine. Activities associated with the greatest risk of illness were disposal of deceased dogs or puppies (RR, 6.9; 95% CI, 1.6–29.7), disposal of deceased cats or dogs (RR, 4.6; 95% CI, 1.1–19.7), providing or assisting with euthanasia of dogs or puppies (RR, 4.3; 95% CI, 1.2–15.4), and providing or assisting with euthanasia of cats or kittens (RR, 3.3; 95% CI, 0.9–11.7) (Table). After aggregating dog- and cat-related activities, disposal of deceased animals (RR, 14.0; 95% CI, 1.9–104.1) and

providing or assisting with euthanasia of animals (RR, 4.6; 95% CI, 1.3–16.9) remained the activities associated with risk of illness.

We found descriptive and analytical evidence that this Q fever outbreak was likely a result of exposure to infected feline parturient products in a population with low prevalence of immunity to *C. burnetii*. Previous studies have demonstrated moderate seroprevalence of *C. burnetii* among Australian domestic cats and dogs and transmission of Q fever from parturient cats has been reported in the United States, Canada, and Australia. It is conceivable that additional events have occurred but gone undetected or unreported due to the lower index of suspicion for Q fever among patients without history of exposure to livestock and the 60% of acute Q fever infections that are asymptomatic.

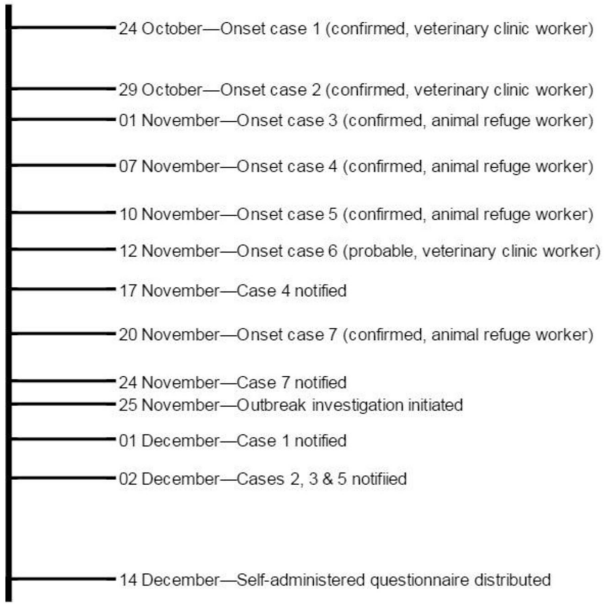
Given our finding that feline birthing events were relatively common in the cat impound, non-immune animal refuge workers in similar workplace settings who are frequently exposed to parturient cats (or dogs) are at increased risk of Q fever infection. We suggest that animal refuge workers be included as a recommended occupation for Q fever vaccine in the Immunisation Handbook. The addition of this group as an at-risk occupation would be timely and reflective of their increased exposure risk.

Please contact us if you would like further details of our investigation findings and analyses.

Kind Regards

Dr Jonathan Malo
Epidemiology Registrar,
Epidemiology & Research Unit
Communicable Diseases Branch,
Queensland Health
e. jonathan.malo@health.qld.gov.au
p: (07) 3328 9178

Dr Stephen Lambert
Medical Director,
Epidemiology & Research Unit
Communicable Diseases Branch,
Queensland Health
e: stephen.lambert@health.qld.gov.au
m: 0405 974 555



Figure—Timeline of Q fever outbreak at an animal refuge and veterinary clinic in southeast Queensland, October–December 2016

Table—Attack rates and risk ratios for workplace-related exposures of Q fever (confirmed and probable) cases and non-cases during an outbreak at an animal refuge and veterinary clinic in southeast Queensland, 15 September–31 October 2016[a]

	Exposed			Unexposed						
	Total	Cases	Attack Rate (%)	Total	Cases	Attack Rate (%)	Risk Ratio	95% CI	P-value
Livestock area									
Visit to livestock area	29	7	24.1	11	0	0.0	—	—	0.07
Contact with any livestock (sheep, goat, horses, poultry)	25	6	24.0	4	1	25.0	1.0	0.2–6.0	0.97
Cleaning of livestock area or animal pens	10	2	20.0	19	5	26.3	0.8	0.2–3.2	0.71
Cat impound									
Visit to cat impound	31	7	22.6	9	0	0.0	—	—	0.12
Direct contact with cats or kittens	28	7	25.0	3	0	0.0	—	—	0.33
Handling of cats or kittens at birth, or present during birthing events	13	4	30.8	18	3	16.7	1.9	0.5–6.9	0.35
Providing or assisting with euthanasia of cats or kittens	9	4	44.4	22	3	13.6	3.3	0.9–11.7	0.06
Disposal of deceased cats or kittens	11	5	45.5	20	2	10.0	4.6	1.1–19.7	0.02
Cleaning of cat impound, cages or changing cat litter	12	3	25.0	19	4	21.1	1.2	0.3–4.4	0.80
Dog impound									
Visit to dog impound	34	7	20.6	6	0	0.0	—	—	0.22
Direct contact with dogs or puppies	32	6	18.8	2	1	50.0	0.4	0.1–1.8	0.29
Handling of dogs or puppies at birth, or present during birthing events	6	1	16.7	28	6	21.4	0.8	0.1–5.3	0.79
Providing or assisting with euthanasia of dogs or puppies	8	4	50.0	26	3	11.5	4.3	1.2–15.4	0.02
Disposal of deceased dogs or puppies	9	5	55.6	25	2	8.0	6.9	1.6–29.7	0.002
Cleaning of dog impound, cages or dog waste	14	3	21.4	20	4	20.0	1.1	0.3–4.1	0.92

[a] The outbreak occurred from October–December 2016 and the workplace-related exposures were reported from 15 September–31 October 2016

Appendix D—Supplementary Table

Table—Attack rates and risk ratios for workplace-related exposures of Q fever cases (confirmed and probable) and susceptible non-cases* during an outbreak at an animal refuge and veterinary clinic in southeast Queensland, 2016†

	Exposed			Unexposed					
	Total	Cases	AR (%)	Total	Cases	AR (%)	RR	95% CI	p-value‡
Livestock area									
Visit to livestock area	20	7	35.0	7	0	0	4.5§	0.6–∞	0.14
Contact with any livestock (sheep, goat, horses, poultry)	18	6	33.3	2	1	50.0	0.7	0.1–3.1	1
Cleaning of livestock area or animal pens	6	2	33.3	14	5	35.7	0.9	0.2–3.5	1
Cat impound									
Visit to cat impound	22	7	31.8	5	0	0	2.8§	0.3–∞	0.28
Direct contact with cats or kittens	21	7	33.3	1	0	0	0.5§	0.01–∞	1
Handling cats/kittens at birth, or present during birthing events	10	4	40.0	12	3	25.0	1.6	0.5–5.5	0.65
Providing or assisting with euthanasia of cats or kittens	9	4	44.4	13	3	23.1	1.9	0.6–6.6	0.38
Disposal of deceased cats or kittens	9	5	55.6	13	2	15.4	3.6	0.9–14.7	0.07
Cleaning of cat impound, cages or changing cat litter	8	3	37.5	14	4	28.6	1.3	0.4–4.4	1
Dog impound									
Visit to dog impound	24	7	29.2	3	0	0	1.4§	0.1–∞	0.55
Direct contact with dogs or puppies	23	6	26.1	1	1	100.0	0.3	0.1–0.5	0.29
Handling dogs/puppies at birth, or present during birthing events	5	1	20.0	19	6	31.6	0.6	0.1–4.1	1
Providing or assisting with euthanasia of dogs	8	4	50.0	16	3	18.8	2.7	0.8–9.2	0.17
Disposal of deceased dogs or puppies	9	5	55.6	15	2	13.3	4.2	1.0–17.2	0.06
Cleaning of dog impound, cages or dog waste	10	3	30.0	14	4	28.6	1.1	0.3–3.7	1

*Susceptible non-cases include individuals who reported receiving Q fever vaccine during the outbreak investigation after screening with intradermal hypersensitivity and complement fixation testing. †The outbreak occurred from October–December 2016 and the workplace-related exposures were reported from 15 September–31 October 2016. ‡Fisher's exact p-value. §Odds ratio and lower bound of the 95% confidence interval calculated using exact logistic regression. AR, attack rate; RR, risk ratio.

(This page left intentionally devoid of content)

III

Establishing a surveillance system for newly acquired hepatitis C infection in Queensland

Table of Contents

Prologue

In Australia, infection with the hepatitis C virus is a nationally notifiable disease in the 'Blood-borne viruses and sexually transmitted infections' group. Notifications of hepatitis C are classified as either 'unspecified' or 'newly acquired'. For notifications to be classified as newly acquired, cases are required to have evidence of one of the following: a negative anti-hepatitis C antibody test within the preceding 24 months, detection of anti-hepatitis C antibody in a child aged 18 to 24 months, or detection of hepatitis C virus by nucleic acid testing in a child aged 3 to 24 months. Alternatively, cases may also be classified as newly acquired if they have had a clinical presentation consistent with acute hepatitis (jaundice, bilirubinuria, or alanine transaminase more than 10 times the normal limit) within the previous 24 months, where other causes of acute hepatitis have been excluded.

At the commencement of my placement, Queensland was the only state that did not identify or report newly acquired cases of hepatitis C to the National Notifiable Disease Surveillance System (NNDSS), with all notifications classified as unspecified. Newly acquired hepatitis C was also the only nationally notifiable disease not reported by Queensland. The lack of reporting of newly acquired cases represented a risk to both those responsible for communicable disease control and reporting, and to public health unit staff, as there was an inability to detect clustering of newly acquired cases and monitor trends in community transmission.

Project role

I worked within the Epidemiology and Research unit to develop a process for identification of newly acquired hepatitis C infections using data linkage to match new notifications of hepatitis C with previous negative anti-hepatitis C virus antibody test results. I also developed enhanced surveillance processes for subsequent follow-up of certain cases by the diagnosing clinician and relevant public health unit staff. The first phase of the project that I was involved in included requesting a change to the Queensland Notifiable Conditions System to allow recording of newly acquired hepatitis C infections, as this was not

previously a disease classification available in the system. I then developed the Stata code to identify cases that had a previous negative anti-hepatitis C antibody test in the public pathology laboratory data. I subsequently developed and piloted a surveillance form to send to diagnosing clinicians to collect information related to reasons for testing and known risk factors for hepatitis C acquisition. Using the information gathered from previous hepatitis C test results and the diagnosing clinician surveillance form, I developed criteria for the follow-up of cases by the relevant public health unit. I also modified the existing enhanced surveillance case report form to align with the enhanced surveillance fields collected for national reporting.

Lessons learned

This project was the most rewarding for me to complete while also being the most challenging. I enjoyed the process of reasoning how the system might work and exploring potential methods that could be implemented. I soon realised I could not develop a perfect system due to constraints with receiving identifying information from private pathology laboratories. My approach then focused on the resources that were available within the Communicable Diseases Branch in order to implement a system that was both feasible and sustainable. The technical aspects of the surveillance system were most interesting to me, but the process of engaging with public health physicians and general practitioners for feedback was likely most useful for my own experience. While engaging stakeholders in such projects is extremely important, it can also be very difficult to receive feedback from those with many other responsibilities and priorities. In this regard, having a 'buy-in' from stakeholders to recognise the importance of the work you are doing is essential. This will be a lesson I take forward with me in my career in public health and epidemiology.

Public health impacts

The establishment of this surveillance system has resulted in the following potential impacts:

- Risk factor data are now routinely collected and reported for identified cases of newly acquired hepatitis C. These surveillance data may be used to

monitor and evaluate public health interventions related to control of hepatitis C

- Implementation of routine follow-up of newly acquired cases of hepatitis C infection where injecting drug use and imprisonment have not been identified as risk factors for transmission. This aspect of the system has the potential to identify threats to public health, allowing for prevention of further disease transmission

Communications

This project resulted in the following communications and dissemination of findings:

- Royal Australasian College of General Practitioners newsletter communication to members regarding the commencement of enhanced follow-up of newly acquired cases of hepatitis C
- Presentation at Queensland public health physicians' face-to-face meetings, October 2016 and June 2017
- Presentation at a Queensland public health nurses face-to-face meeting, June 2017
- Oral presentation at Public Health Association of Australia 23rd Communicable Disease Control Conference, Melbourne, 28 June 2017

Core activity requirements

This project meets the following core MAE activity requirements:

- Establish or evaluate a disease surveillance system
- Presentation at a national scientific conference

Acknowledgements

I acknowledge the special contributions of Communicable Diseases Branch staff for their assistance in developing and implementing this system: Mohana Rajmokan, Andrew Lockhart, Belinda Eagle, Mayet Jayloni, and John Marquess. I also acknowledge the public health physicians, public health unit staff, and staff at the general practices who assisted with providing feedback and input into the various aspects of the system.

Abstract

Background: Infection with hepatitis C virus is a nationally notifiable condition in Australia. Cases with either laboratory or clinical evidence of their infection being acquired within the previous 24 months are classified as newly acquired infections, while all other cases are classified as unspecified. Prior to 2016, Queensland was the only state not to identify or report newly acquired hepatitis C infections. The primary objectives of this project were to establish a surveillance system to identify and follow-up newly acquired hepatitis C infections in Queensland.

Methods: I established a surveillance system that used data linkage to match previous public laboratory negative anti-hepatitis C antibody test results with new notifications of hepatitis C. The data linkage process was performed retrospectively for hepatitis C notifications from 2011 to 2016, and was integrated into the Queensland weekly notification process in January 2017. I also developed an enhanced surveillance process for cases identified as newly acquired infections who were not imprisoned at the time of their diagnosis or within the previous 24 months. For these cases, a surveillance form was sent to the diagnosing clinician to collect information regarding reasons for testing and risk factors for acquisition. Where newly acquired infections did not have imprisonment or injecting drug use identified as risk factors, further follow-up by local public health units occurred to assess possible routes of transmission and the presence of any ongoing threat to public health.

Results: From 2011 to 2016, a total of 14,975 hepatitis C cases were notified to the Queensland State Department of Health, of which 1,740 (12%) were identified as newly acquired infections. As part of weekly notification activities, the data linkage process took approximately 30 minutes to complete. In the first half of 2017, 62 diagnosing clinician forms were distributed, of which 46 (79% response rate) were returned. Six cases of newly acquired infection did not have imprisonment or injecting drug use identified as risk factors by the diagnosing clinician and required further follow-up by the staff from their local public health unit. After PHU follow-up, all of these cases were assessed to have likely acquired their infections through IDU.

Conclusions: Data linkage provided an efficient and sustainable process to identify newly acquired hepatitis C infections. Legislative changes that provide access to private laboratory negative test results would improve case ascertainment and the overall usefulness of the system.

Introduction

Infection with hepatitis C virus (HCV) is a major cause of chronic liver disease worldwide. In Australia, over 200,000 people are living with chronic hepatitis C infection, with an estimated 47,000 residing in Queensland.[1] Transmission of HCV most commonly occurs through contact with infected blood products, usually as a result of injecting drug use (IDU).[2] Historically, the majority of individuals who become infected with HCV developed chronic hepatitis C, while approximately one-quarter of individuals spontaneously clear the virus.[3] However, new treatments options—publicly subsidised for all people living with hepatitis C in Australia—clear the infection in 79–95% of cases, varying according to the infecting HCV genotype and treatment regimen.[4] However, as only 10–30% of acute HCV infections are symptomatic, most commonly with fever, jaundice, abdominal pain, fatigue, myalgia, dark urine, nausea, vomiting, or loss of appetite,[5,6] diagnosis and treatment are often delayed.

Cases of hepatitis C that have recently acquired their infection provide the opportunity to ascertain the most likely mode of transmission, enabling the monitoring of recent trends in risk factors for acquisition of HCV. Accurate and timely information regarding those with newly acquired HCV infections also allows for the identification of priority groups for public health interventions and treatment. The availability and funding of highly curative treatments has raised the possibility of HCV elimination, increasing the importance of HCV surveillance activities. While most cases acquire their infections as a result of IDU practices, non-IDU-related transmission does occur.[7-9] Identification and follow-up of incident hepatitis C infections can potentially detect cases or clusters of non-IDU-related HCV transmission, enabling a public health response.

Hepatitis C surveillance in Australia

Hepatitis C is a nationally notifiable disease in Australia, with all states and territories reporting cases to the National Notifiable Diseases Surveillance System (NNDSS). Cases are classified as either ‘unspecified’ or ‘newly acquired.’

The Communicable Diseases Network Australia (CDNA) national case definition for newly acquired hepatitis C is presented in Box 1.[10] All confirmed hepatitis C notifications that do not meet the newly acquired case definition are classified as unspecified. National reporting fields for enhanced surveillance of newly acquired hepatitis C cases include reasons for testing and identified risk factors for HCV transmission (Appendix A).

Box 1—Communicable Disease Network Australia national case definition for hepatitis C (newly acquired)[10]

Reporting
Only confirmed cases should be notified.
Confirmed case
A confirmed case requires either: 1. Laboratory definitive evidence *OR* 2. Laboratory suggestive evidence *AND* clinical evidence.
Laboratory definitive evidence
1. Detection of anti-hepatitis C antibody from a person who has had a negative anti-hepatitis C antibody test recorded within the past 24 months *OR* 2. Detection of hepatitis C virus by nucleic acid testing from a person who has a negative anti-hepatitis C antibody test result currently, or has had, within the past 24 months *OR* 3. Detection of anti-hepatitis C antibody from a child aged 18 months to 24 months *OR* 4. Detection of hepatitis C virus by nucleic acid testing in a child aged 3 months to 24 months.
Laboratory suggestive evidence
Detection of anti-hepatitis C antibody, or hepatitis C virus by nucleic acid testing in a patient with no prior evidence of hepatitis C infection.
Clinical evidence
Clinical hepatitis within the past 24 months (where other causes of acute hepatitis have been excluded) defined as: 1. Jaundice *OR* 2. Bilirubin in urine *OR* 3. Alanine transaminase (ALT) ten times the upper limit of normal.

Queensland

In Queensland, cases of hepatitis C are notified by pathology laboratories to the Queensland State Department of Health. Hepatitis C is listed as a 'pathological diagnosis notifiable condition' and 'controlled notifiable condition' in the *Public Health Regulation 2005*.[11] Under the *Public Health Act 2005*,[12] pathology laboratories must notify the Department of Health when examination of a

specimen indicates the patient has a pathological diagnosis of a notifiable condition. For controlled notifiable conditions, the *Act* provides additional regulatory powers, such as chief executive's orders or detention orders, to stop the transmission of the condition to other persons.

Prior to 2016, Queensland did not have a surveillance system to identify or report cases of newly acquired hepatitis C to the NNDSS, with all notifications of hepatitis C classified as unspecified. Enhanced surveillance and follow-up of newly acquired hepatitis C infections therefore also did not occur during this period. From 2011-2015, Queensland reported an average of 2,200 unspecified hepatitis C notifications annually, the second highest case-burden of all states and territories after New South Wales. Due to the high number of hepatitis C notifications received, manual review of the testing history for each notification was not a feasible method to identify newly acquired infections. Additionally, there is no legislative requirement for clinicians to notify the Department of Health upon diagnosing HCV infection.

A large proportion of medical laboratory testing in Queensland is performed by the state public pathology laboratory, Pathology Queensland. Pathology Queensland provides pathology services to all Queensland public hospitals, prisons, and certain community health services (e.g. alcohol and drug services, sexual health clinics). Healthcare professionals working in public hospitals, public health units (PHUs), and the Department of Health are able to access Pathology Queensland test results through the state-wide electronic pathology results software program (AUSLAB). Two private pathology laboratories, Sullivan Nicolaides Pathology and Queensland Medical Pathology, also perform a considerable portion of the medical laboratory testing within the state, and are used largely by general practitioners and private healthcare providers.

As a decentralised health system, PHUs are responsible for the follow-up and enhanced surveillance of notifiable diseases within their respective jurisdictions, with 13 PHUs operating in 16 Hospital and Health Services across the state. However, due to the high case numbers and absence of a system to identify

newly acquired infections, notifications of hepatitis C are not routinely followed-up by PHUs.

Other states and territories

In other Australian jurisdictions, identification of newly acquired cases is performed through a combination of accessing previous pathology laboratory testing data, obtaining case information from diagnosing clinicians, and follow-up of certain cases according to their age, as part of enhanced surveillance. Previous efforts in Australia to improve hepatitis C surveillance have identified between 1-8% of notifications as newly acquired, after appropriate follow-up.[2,13-18]

In Victoria, the *Public Health and Wellbeing Act 2008* requires diagnosing medical practitioners to notify the Victorian Department of Health & Human Services (DHHS) of notifiable conditions.[19] For hepatitis C, diagnosing medical practitioners are required to complete a written notification of hepatitis C to DHHS within five days of diagnosis.[20] The hepatitis C notification form contains information regarding classification of hepatitis C (i.e. newly acquired or unspecified), patient details and demographics, risk factors, and reasons for testing. Follow-up of notifications occurs in cases identified as newly acquired, aged 30 years or younger, healthcare workers, where the doctor's notification raise public health concerns, and in those with no identified high-risk exposures other than having undergone skin penetrating procedures (e.g. tattooing, body piercing).

In Western Australia, the public pathology laboratory (PathWest) notifies the Department of Health if a patient has had a negative anti-HCV antibody test within two years of the notifying test result. PathWest services correctional centres in WA and therefore a large number of newly acquired cases are identified from the prison population. Additionally, enhanced surveillance is performed on a random sample of 30% of the unspecified cases.

In the Northern Territory, enhanced surveillance forms are faxed to diagnosing clinicians of hepatitis C cases who have not previously been notified. The

information provided by the diagnosing clinician is used to determine if cases meet the newly acquired case definition. Further investigation is performed for all newly acquired infections to determine the most likely source of infection and whether any further public health action is required.

Challenges with hepatitis C surveillance

There are inherent challenges related to the identification and surveillance of newly acquired hepatitis C infections. As 70 to 90% of acute infections are asymptomatic, only a small proportion of cases will be diagnosed during the acute phase of illness (i.e. when symptoms might be most likely to be apparent), when accurate ascertainment of risk factors and attribution of disease acquisition routes could be successful. As a result, chronic HCV infections may go undiagnosed and untreated for considerable periods of time. Additionally, in instances when cases develop acute hepatitis and are subsequently diagnosed with HCV infection, identifying these people as having a newly acquired infection may not occur due to the lack of legislative requirements for clinicians to provide this information to the relevant PHU or State Department of Health.

Due to resource limitations, accessing previous negative hepatitis C test results, in particular those performed at private pathology laboratories or interstate, is not always possible or feasible for PHU or CDB staff. Where multiple pathology laboratories operate, patients may often undergo testing through different laboratories and results may not be readily accessible to PHU staff responsible for enhanced surveillance and follow-up. For laboratory tests by Pathology Queensland, individuals are assigned different unique person identifiers for each hospital, health clinic, or correctional centre they attend, further complicating the process of manually searching individual testing history. Furthermore, due to the potential stigmatisation of HCV infection, names of patients are frequently anonymity coded in testing documentation. Most commonly, these anonymity codes consist of the first two letters of the patient's first and last names, or a combination thereof. This further complicates the matching of new notifications with previous HCV test results.

Finally, a case definition requiring evidence of seroconversion necessitates that individuals have previously been tested for HCV in the past 24 months, which is unlikely to occur in the general population. Groups who are routinely screened for HCV, such as people who inject drugs (PWID) and those who are imprisoned, are therefore the most likely to be identified by this case definition. Individuals who acquire HCV and who do not inject drugs are less likely to have undergone previous HCV screening, and are therefore less likely to be identified as a newly acquired infection in the absence of acute hepatitis. Such cases are important to identify through the process of enhanced surveillance as their mode of HCV acquisition is more likely to represent a risk to the public (such as a healthcare acquired infection), requiring further investigation and public health actions.

Aim and objectives

The aim of this project was to create an efficient and sustainable system for the identification and follow-up of newly acquired hepatitis C infections in Queensland.

The key objectives of the surveillance system and project were to:

- identify cases of newly acquired hepatitis C infection for state and national reporting, both retrospectively to establish baseline trends, and prospectively as part of weekly notifications reporting.
- compare the demographics of notifications identified as newly acquired hepatitis C infections with those that remained classified as unspecified.
- compare the number, rates, and proportion of total hepatitis C notifications identified as newly acquired with other states and territories.
- establish a process where reasons for testing and risk factors for HCV transmission are collected for newly acquired infections.
- prioritise cases of newly acquired hepatitis C infections for enhanced surveillance and follow-up by PHUs.
- conduct an informal evaluation of the established system to ensure long-term sustainability.

Methods

Scoping and overview of system development

The absence of a pre-existing hepatitis C surveillance system necessitated the development of a system to operate within the resources, capacity, and legislative contexts in Queensland. The design of the system was therefore influenced by the high number of weekly hepatitis C notifications, a lack of legislative requirements for clinicians to notify the Queensland State Department of Health upon diagnosing HCV infections, and the ability to extract case information from the state Notifiable Conditions System (NOCS) and laboratory test results from AUSLAB in CDB.

The key processes in development of the system included engaging relevant stakeholders, developing and applying case definitions, changes to NOCS to allow for the coding of newly acquired cases, developing a data linkage process for matching of new notifications with previous pathology test results, a retrospective identification of newly acquired infections, incorporating data linkage processes into routine notification activities within the CDB, development and implementation of a diagnosing clinician surveillance form, and developing an enhanced surveillance and follow-up process for certain newly acquired cases to be completed by PHU staff.

Stakeholder engagement

As no previous surveillance system for newly acquired hepatitis C infections existed at the commencement of this project, and follow-up of unspecified hepatitis C infections by PHU staff did not occur, it was necessary to consult relevant stakeholders (Box 2) during the development and implementation of the surveillance system. Stakeholders were engaged to inform them of changes to hepatitis C surveillance processes, gain input related to their roles and responsibilities in the surveillance and follow-up of hepatitis C infections, and ensure the developed system was both acceptable and sustainable. Part of the stakeholder engagement process involved presentations at Queensland public

health physician face-to-face meetings in October 2016 and June 2017, and at a Queensland public health nurse face-to-face meeting in June 2017.

Box 2—Stakeholders and their roles in surveillance of hepatitis C infections in Queensland

Communicable Diseases Branch staff
State-wide surveillance
Reporting to the National Notifiable Diseases Surveillance System
Communication with Public Health Units
Public Health Unit staff
Enhanced surveillance of newly acquired cases
Reporting to the Communicable Diseases Branch
Investigation of potential threats to public health
Clinicians
Reporting information of newly acquired cases to Communicable Diseases Branch
Patient care

To inform clinicians that they may be asked to provide information regarding reasons for testing and risk factors of patients they diagnose with newly acquired hepatitis C, a notice was placed in the newsletter of the Queensland branch of the Royal Australasian College of General Practitioners (Box 3).

Box 3—Notice from the Royal Australasian College of General Practitioners to Queensland Fellows and trainees regarding faxing of surveillance forms to diagnosing clinicians of newly acquired cases of hepatitis C

Notices to Queensland Fellows and trainees – from the Communicable Diseases Branch of Queensland Health

Surveillance system for newly acquired cases of hepatitis C

The Communicable Diseases Branch of Queensland Health is implementing a surveillance system for newly acquired cases of hepatitis C (infection acquired within the previous 24 months). As part of this process, we will soon commence faxing surveillance forms to the diagnosing clinicians of these cases requesting information on reasons for testing and presence of known risk factors for hepatitis C infection.

Queensland Government

For further information, please contact Dr Stephen Lambert, Medical Director, Epidemiology & Research Unit at stephen.lambert@health.qld.gov.au.

Notification method

Laboratory notifications of hepatitis C cases are transmitted electronically to the NOCS electronic database in the State Department of Health. A notification is triggered by either detection of anti-HCV antibody or detection of HCV genetic

material by nucleic acid testing. After one notification has been created for an individual, no new notifications will occur as a result of subsequent positive HCV test results in the same individual. All new notifications of hepatitis C are automatically initially classified as unspecified by NOCS.

Newly acquired case definitions

The CDNA case definition requires confirmed cases of newly acquired hepatitis C to have either laboratory definitive evidence or laboratory suggestive evidence and clinical evidence (Box 1).

Laboratory definitive evidence

The laboratory definitive evidence case definition, requiring evidence of a previous negative anti-HCV antibody within 24 months in a case of confirmed HCV infection, was used to classify notifications as newly acquired.

Clinical evidence

From 2017, the clinical evidence definition of alanine transaminase (ALT) levels greater than 10 times the upper limit of normal was used to identify cases of potentially newly acquired infection. Other potential causes of acute hepatitis were identified through the diagnosing clinician surveillance form. The clinical evidence definition was not used to identify newly acquired infections prior to 2017 as it was not feasible to identify and contact all diagnosing clinicians in order to exclude other causes of acute hepatitis.

Queensland Pathology defines the upper limit of normal for ALT as <45 units/litre (u/L) for men and <34 u/L for women; therefore, an ALT level ≥450 u/L for men and ≥340 u/L for women defined 10 times the upper limit of normal. To limit the identification of individuals with chronic hepatitis, only those with evidence of acutely elevated ALT levels were considered as potentially newly acquired infections. We defined the acute period as 56 days before to 28 days after the collection of the notifying specimen. This period was chosen as, during acute HCV infection, ALT levels generally rise one to two weeks following the presence of detectable HCV RNA, and up to eight weeks

before anti-HCV antibodies become detectable.[5,6,21,22] Individuals with elevated ALT levels both during and before the acute period were considered to have chronically elevated ALT levels and less likely to represent acute hepatitis; these cases were therefore not followed-up as potential newly acquired infections.

The clinical evidence definitions involving presence of jaundice or bilirubinuria were not used as this clinical information was not easily accessible or available, and therefore not feasible to include in the design of the surveillance system.

Changes to the Notifiable Conditions System

A notification category for newly acquired hepatitis C was created in NOCS to allow for coding of the cases identified through the system as meeting the case definition. Enhanced surveillance fields were added to reflect the information being collected in the diagnosing clinician surveillance form and updated hepatitis C case report form (CRF).

Data extraction and linkage

Linkage of AUSLAB testing and NOCS notification data

Hepatitis C (unspecified) notifications with onset dates from 01 January 2011 to 31 December 2016 were extracted from NOCS. Negative anti-hepatitis C antibody test results collected between 01 January 2009 and 31 December 2016 were extracted from AUSLAB. NOCS and AUSLAB data were imported into Stata 14.1 (StataCorp, USA) and matching was performed using the *reclink*[23] package, with full name, sex, date of birth, first two letters of first name, and first two letters of last name as linking variables. Probability matching was only performed on cases with same date of birth. Matching weights and non-matching weights of linking variables are provided in Box 4. A probability match score of ≥0.80 was used to define positive matches. The matching weights were chosen after trialling multiple combination of weights and manually reviewing the linkage results for false positive and false negative matches above and below the 0.80 probability match score, respectively. Positive matches with anonymity coded names (e.g. first two letters of last name, first two letters of first name) recorded in either the NOCS or AUSLAB patient details were considered a true

match if each of date of birth, sex, first two letters of first name, and first two letters of last name were exact matches. Positive matches were manually reviewed by Data Services staff to ensure sufficient information was present to indicate a true match. The notification classification of all true matches meeting the newly acquired case definition was changed to newly acquired by Data Services staff.

Box 4—Matching and non-matching weights of linking variables used for probabilistic matching* of hepatitis C notifications with previous negative anti-HCV antibody test results in Stata using reclink23 package

Linking variable	Matching weight†	Non-matching weight†
Full name	12	6
First 2 letters of first name	6	6
First 2 letters of last name	6	8
Date of birth‡	10	10
Sex	2	6

*A probability match score of ≥0.80 used as the cut-off for a positive match. †Matching and non-matching weights have a possible range of 1–20. ‡Probability match scores only generated for records with the same date of birth.

Notifications in those aged younger than 24 months of age at the time of diagnosis were manually reviewed to determine if they met the age-specific requirements of the national case definition (Box 1, laboratory definitive evidence criteria 3 and 4).

Matched cases were identified as being imprisoned at the time of diagnosis if a correctional centre was listed as the address for the patient received by NOCS via the laboratory notification process. Cases were considered to have been imprisoned in the previous 24 months if any previous negative anti-HCV antibody or elevated ALT test extracted from AUSLAB had a correctional centre recorded as the patient address.

Weekly notification process

The above extraction and linkage process was integrated into the Queensland weekly notifiable conditions reporting process within the CDB in January 2017. For cases notified from 01 January 2017, the AUSLAB data extraction included records with elevated ALT levels in addition to negative hepatitis C antibody tests. The sustainability of the system was assessed according to the required

time for the extraction and linkage process, and the number of surveillance forms faxed to diagnosing clinicians.

I prepared a Work Instruction (Appendix B) for CDB staff detailing the data extraction and linkage processes. I also created a Stata .do file that was used to perform the linkage each week by a member of the Data Services or the Epidemiology & Research teams. Positive matches were exported into a Microsoft Excel spreadsheet and manually reviewed for sufficient matching information by Data Services staff. True matches were updated to hepatitis C (newly acquired) in NOCS. The date of the most recent negative anti-HCV antibody test, presence of imprisonment at the time of diagnosis or in the previous 24 months, and if the case was identified through acutely elevated ALT levels were recorded in the relevant NOCS enhanced surveillance fields.

Data analysis

Newly acquired and unspecified infections from 2011 to 2016 were compared by age group (younger than 30 years, 30 years or older), sex, and imprisonment status at the time of diagnosis using the chi-square test of proportions, with a p-value <0.05 considered significant. Analyses were performed in Stata 14.1.

Comparison with other states & territories

Newly acquired and unspecified hepatitis C notification counts from 2011 to 2016 were compared to those in other states and territories using publicly available reports from the NNDSS.[24] Notification rates for states and territories during this period were calculated using mid-year estimated resident population (ERP) estimates from the Australian Bureau of Statistics (ABS).[25]

Diagnosing clinician surveillance form

I developed a surveillance form to fax to the diagnosing clinicians of newly acquired hepatitis C notifications (Appendix C). The surveillance form was used to collect information regarding reasons for hepatitis C testing and identified risk factors for acquiring HCV infection. For cases identified as potentially newly acquired infections identified as such by the presence of acutely elevated

ALT levels, the diagnosing clinician surveillance form included an extra question regarding other possible causes for the elevated ALT levels, such as other viral hepatitis, hepatotoxic drugs, or other liver conditions.

In developing the surveillance form, I engaged primary care clinics and public health physicians to provide feedback regarding the information being collected, design of the form, and ease of use. To identify clinicians that would likely be completing the form, I reviewed hepatitis C notifications from 2011 to 2015 and identified primary care clinics that diagnosed the highest numbers of hepatitis C notifications. A draft of the surveillance form was sent to three of these primary care clinics and PHU public health physicians for feedback, which was incorporated into the final version of the form.

Enhanced surveillance case report form

A Queensland enhanced surveillance CRF had previously been developed in 2011 for newly acquired hepatitis C. As newly acquired infections were not previously being identified or followed up, the previous CRF was not in use. I updated the enhanced surveillance CRF (Appendix D) to align with fields reported to the NNDSS and to collect useful information to assist in detecting cases, or clusters of cases, not related to injecting drug use.

Evaluation

A formal evaluation of the surveillance system was not undertaken as this was not possible within the timeframe of my MAE placement. However, the strengths and limitations of the surveillance system are addressed in the Discussion section in relation to the system attributes defined by the *Centers for Disease Control and Prevention Guidelines for Evaluating Public Health Surveillance Systems*.[26]

Results

Timeline

The timeline of the establishment of the surveillance system from initial scoping until final implementation is shown in Figure 1.

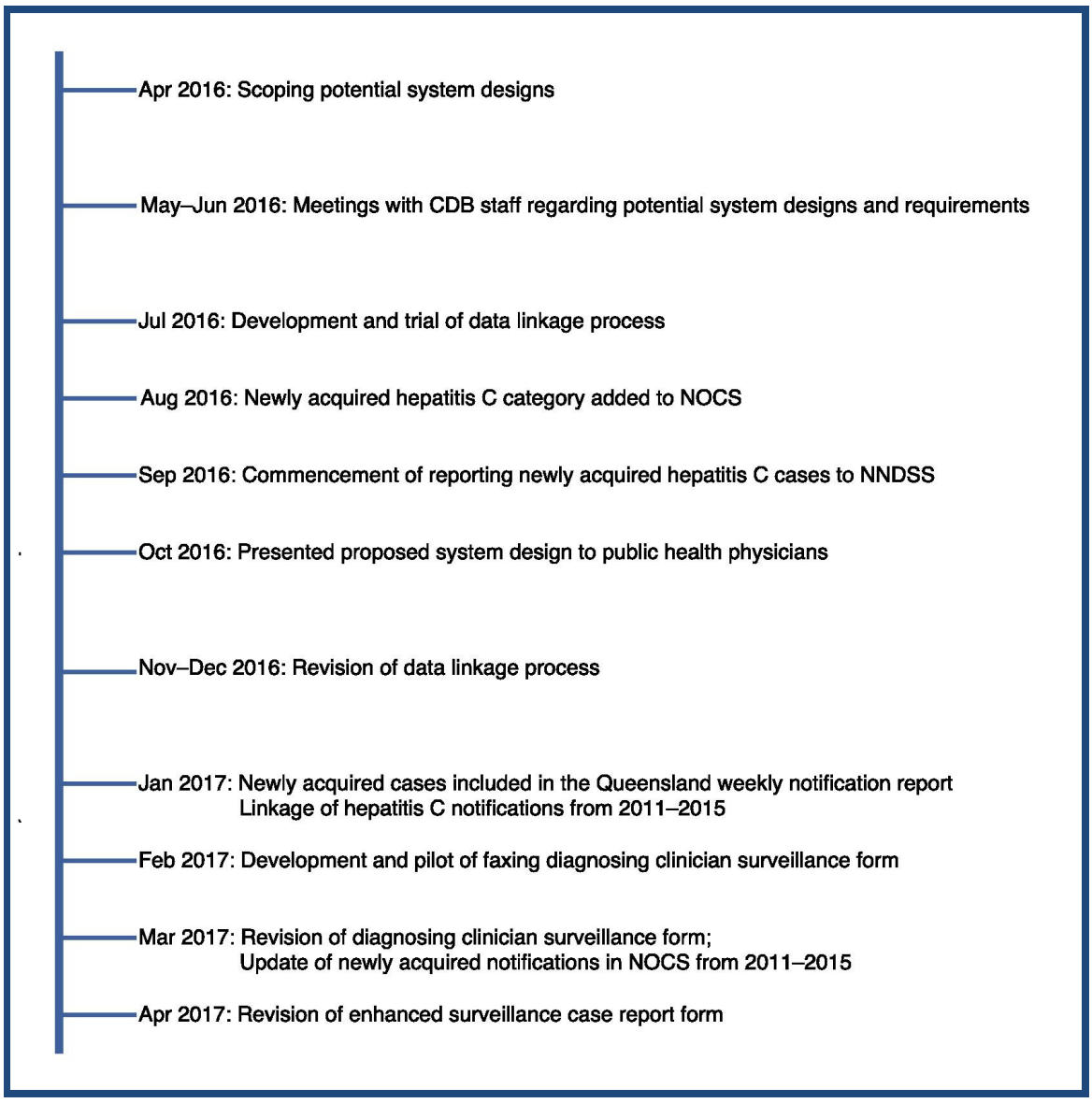


Figure 1—Timeline of the development and implementation of a surveillance system to identify and follow-up notifications of newly acquired hepatitis C infections in Queensland. CDB, Communicable Diseases Branch; NOCS, Notifiable Conditions System; NNDSS, National Notifiable Diseases Surveillance System.

System design

The processes involved in the operation of the surveillance system, including identification of newly acquired hepatitis C infections, completion of surveillance forms by diagnosing clinicians, and enhanced surveillance and follow-up of cases by PHUs, are shown in Figure 2.

Linkage of AUSLAB testing and NOCS notification data

From 2011 to 2016, there were 14,975 notifications of hepatitis C received in Queensland. Matching of notifications to previous anti-HCV antibody testing history identified 1,735 (12%) infections as newly acquired. Three additional notifications were classified as newly acquired in children aged younger than 24 months, with HCV detected by nucleic acid testing. The demographic characteristics of newly acquired and unspecified hepatitis C notifications during this period are shown in Table 1. The data linkage algorithm resulted in a false-positive match rate of less than one percent, and occurred due to similarity between full names and an identical date of birth.

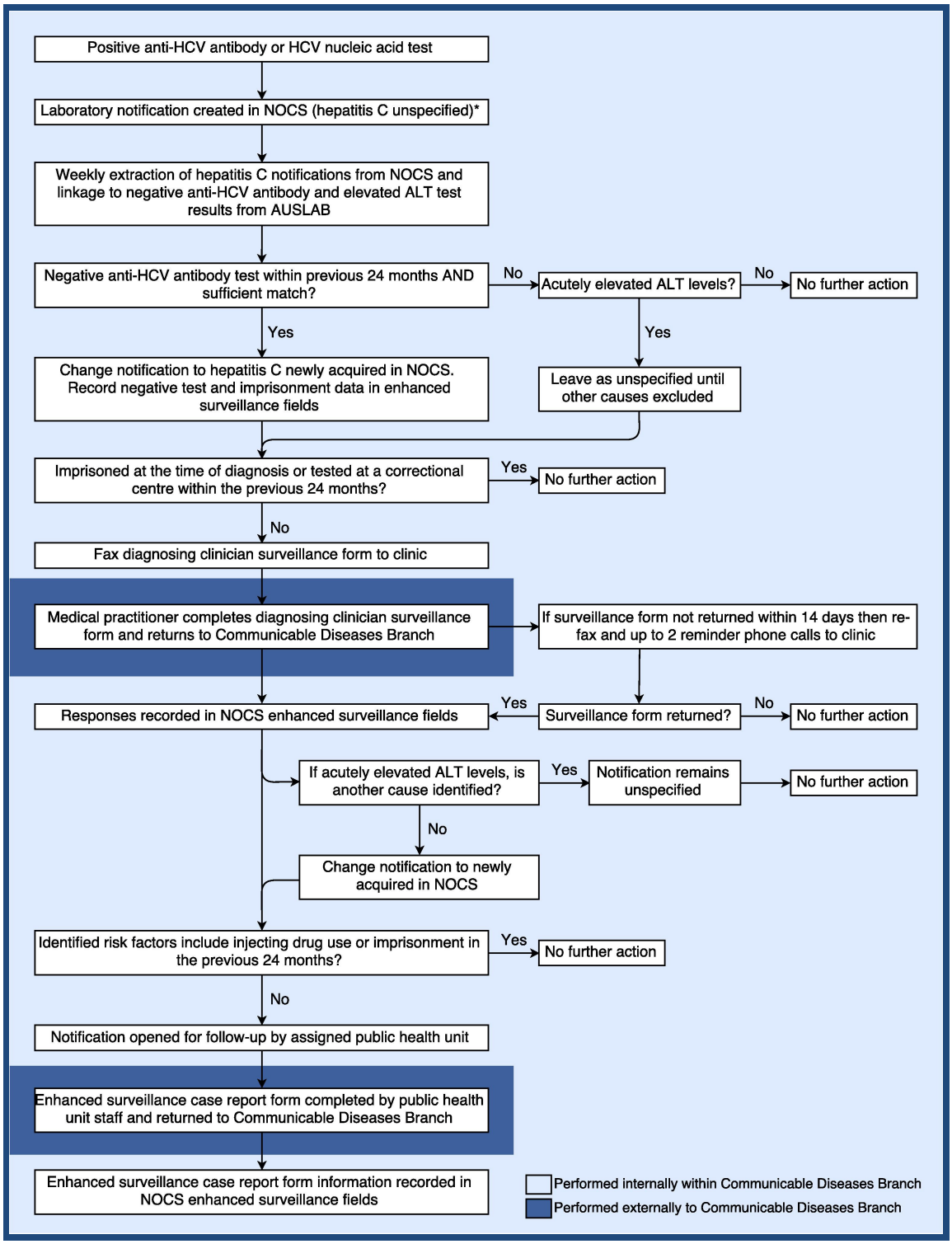


Figure 2—Design of surveillance system to identify and follow-up cases of newly acquired hepatitis C infections in Queensland. ALT, alanine transaminase; AUSLAB, Queensland Pathology results software; HCV, hepatitis C virus; NOCS, notifiable conditions system.

Table 1—Characteristics of newly acquired and unspecified hepatitis C notifications by age, sex, imprisonment status, and year of notification, Queensland, 2011–2016

	Newly acquired		Unspecified		Total	
	n=1,735	(%)	n=13,240	(%)	n=14,975	(%)
Age group (years)						
<2	3	(0.2)	0	(0.0)	3	(0.0)
2–19	167	(9.6)	359	(2.7)	526	(3.5)
20–29	956	(55.1)	2,699	(20.4)	3,655	(24.4)
30–39	446	(25.7)	3,739	(28.2)	4,185	(27.9)
40–49	128	(7.4)	3,208	(24.2)	3,336	(22.3)
50–59	26	(1.5)	2,483	(18.8)	2,509	(16.8)
≥60	9	(0.5)	752	(5.7)	761	(5.1)
Sex						
Male	1,319	(76.0)	8,637	(65.2)	9,956	(66.5)
Female	416	(24.0)	4,603	(34.8)	5,019	(33.5)
Imprisoned at time of notification						
Yes	831	(47.9)	1,634	(12.3)	2,465	(16.5)
No	904	(52.1)	11,606	(87.7)	12,510	(83.5)
Year of notification						
2011	210	(12.1)	2,149	(16.2)	2,359	(15.8)
2012	237	(13.7)	2,080	(15.7)	2,317	(15.5)
2013	275	(15.9)	2,158	(16.3)	2,433	(16.2)
2014	267	(15.4)	2,282	(17.2)	2,549	(17.0)
2015	371	(21.4)	2,174	(16.4)	2,545	(17.0)
2016	375	(21.6)	2,397	(18.1)	2,772	(18.5)

Males made up a significantly higher proportion of newly acquired notifications compared to the proportion of unspecified notifications (76% vs. 65%; χ^2, 80.1; p<0.001). The proportion of notifications received in individuals who were imprisoned at the time of diagnosis was significantly higher in those identified as newly acquired compared to those classified as unspecified (48% vs. 12%; χ^2, 1410.2; p<0.001). The proportion of cases aged younger than 30 years was significantly higher among those notifications identified as newly acquired compared to unspecified (65% vs. 23%; χ^2, 1331.4; p<0.001).

Comparison with other states and territories

From 2011 to 2016, there were 4,254 notifications of newly acquired hepatitis C in Australia, representing 7% of all (unspecified and newly acquired) national hepatitis C notifications. The crude annual number of newly acquired notifications was highest in Queensland (Table 2), with Queensland accounting for 41% of newly acquired notifications Australia-wide during this period. Within each state, the percentage of all hepatitis C notifications reported as newly acquired was highest in Western Australia (12%), followed by Queensland (12%). Since 2012, Western Australia and Queensland reported the highest newly acquired notification rates, with the lowest reported in New South Wales and the Northern Territory (Table 3). The Northern Territory reported the highest unspecified notification rates, while the lowest was reported in South Australia.

Results of the weekly notification process

Extracting notification data from NOCS, updating anti-HCV antibody testing data from AUSLAB, and performing data linkage in Stata required approximately 30 minutes as part of weekly notifiable conditions reporting.

From 01 January 2017 to 30 June 2017, there were 1,183 new notifications of hepatitis C in Queensland, of which 148 (13%) were identified as newly acquired, representing an average of 5.7 newly acquired cases per week. Of these, 145 (98%) were identified through previous negative anti-HCV antibody test results and 3 (2%) were identified through acutely elevated ALT levels. There were an additional 15 potentially newly acquired cases identified through acutely elevated ALT levels that remained classified as unspecified. These 15 cases either had other causes for acute hepatitis identified through the diagnosing clinician surveillance form or other causes were not able to be excluded because the surveillance form was not returned.

Table 2—Number and percentage of all newly acquired hepatitis C notifications identified as newly acquired by state and territory, 2011–2016

	Crude newly acquired hepatitis C notifications							Percentage of hepatitis C notifications reported as newly acquired						
	2011	2012	2013	2014	2015	2016	2011–16	2011	2012	2013	2014	2015	2016	2011–16
ACT	10	15	16	11	13	15	80	5.3	10.3	8.7	6.3	6.9	8.1	7.5
NSW	51	50	43	33	30	22	229	1.5	1.5	1.2	0.9	0.8	0.5	1.1
NT	3	0	1	2	4	2	12	1.4	0.0	0.4	1.1	2.0	0.9	1
QLD	210	237	275	267	371	375	1,735	8.9	10.2	11.3	10.5	14.6	13.6	11.6
SA	32	78	61	45	43	41	300	6.2	15.2	11.6	9.1	8.6	7.8	9.8
TAS	27	23	19	14	26	23	132	11.8	8.8	8.3	6.1	10.0	8.9	9
VIC	166	178	132	179	146	119	920	7.3	8.1	5.9	8.1	6.3	4.7	6.7
WA	120	128	125	164	183	121	841	11.1	11.3	9.8	14.3	16.0	9.7	12

Table 3—Newly acquired and unspecified hepatitis C annual notification rates by state and territory, 2011–2016

	Newly acquired rate (per 100,000)							Unspecified rate (per 100,000)						
	2011	2012	2013	2014	2015	2016	2011–16	2011	2012	2013	2014	2015	2016	2011–16
ACT	2.7	4.0	4.2	2.9	3.3	3.8	3.5	48.4	34.6	44.1	42.6	44.7	42.9	42.9
NSW	0.7	0.7	0.6	0.4	0.4	0.3	0.5	45.9	44.1	47.2	47.1	46.6	54.7	47.7
NT	1.3	0.0	0.4	0.8	1.6	0.8	0.8	88.6	81.0	105.1	73.1	80.1	88.9	86.1
QLD	4.7	5.2	5.9	5.7	7.8	7.7	6.2	48.0	45.5	46.4	48.3	45.5	49.5	47.2
SA	2.0	4.7	3.7	2.7	2.5	2.4	3.0	29.5	26.2	27.7	26.5	27.0	28.3	27.5
TAS	5.3	4.5	3.7	2.7	5.0	4.4	4.3	39.5	46.7	40.9	42.2	45.3	45.1	43.3
VIC	3.0	3.2	2.3	3.1	2.5	2.0	2.6	38.1	36.0	36.5	34.7	36.4	40.1	37.0
WA	5.1	5.3	5.0	6.4	7.1	4.6	5.6	40.9	41.4	45.8	38.4	37.1	43.0	41.1

Diagnosing clinician surveillance form

From 13 February to 30 June 2017, there were 62 surveillance forms sent to diagnosing clinicians related to people with newly acquired infections. Forty-nine (79% response rate) diagnosing clinician forms were completed and returned. Of these, six did not have injecting drug use or imprisonment in the previous 24 months identified as risk factors. For the 13 diagnosing clinician forms not returned, 10 (77%) had a history of injecting drug use identified in the electronic medical records. The three remaining cases with unreturned diagnosing clinician forms were not returned despite further requests to complete the form, as per the system design (Figure 2).

Enhanced surveillance

The six cases of newly acquired infection without injecting drug use or imprisonment identified as risk factors were followed-up by staff from the relevant PHUs using the enhanced surveillance case report form. All six cases were identified by the relevant PHUs as likely IDU-related HCV infections.

Discussion

This project resulted in the successful implementation of a new surveillance system to identify and report newly acquired infections of hepatitis C virus in Queensland. An enhanced surveillance process was also implemented to gather risk factor data from diagnosing clinicians and, where required, follow-up by PHU staff. The retrospective identification of newly acquired infections from 2011 to 2016 has established baseline information on newly acquired notification rates, allowing for the monitoring of trends in HCV acquisition. This is of particular importance given the recent introduction and availability of highly effective curative treatments for HCV infection.

The system identified relatively high proportions and rates of newly acquired HCV infections when compared with other states and territories. This can largely be attributed to the process of probability matching notification data with previous pathology test results, which provided an accurate and efficient method of identifying newly acquired infections. To our knowledge, Queensland is the only state to use data linkage for the surveillance of newly acquired HCV infections. Given the benefits of data linkage over manual review processes or relying on clinician information to identify newly acquired infections, if this process were to be implemented by other states and territories, it would likely result in improved case ascertainment and efficiency for their respective surveillance processes.

Our system identified nearly half of all newly acquired HCV infections were imprisoned at the time of diagnosis, approximately three times the proportion of unspecified cases. A major contributor to this is likely to be that many prisoners are screened through Queensland Pathology services for HCV and other blood-borne viruses upon prison entry, and are therefore more likely to have previous HCV testing history to enable identification of newly acquired infections. Additional contributing factors to the high proportion of imprisoned cases may also relate to the fact that Queensland has the second highest total number of incarcerations (after NSW), the third highest total number of incarcerations for illicit drug offences (after NSW and Victoria), the highest

number of both sentenced and unsentenced prisoners for possession or use of illicit drugs, and the third highest proportion of prisoners with previous imprisonment (after ACT and NT).[27] These prisoner statistics likely contribute to both the high overall number and proportion of imprisoned newly acquired HCV infections identified.

Usefulness

The established surveillance system was successful in meeting the objectives defined previously in this Chapter. Estimates of the number of newly acquired infections in Queensland, and collection of risk factor data, are now incorporated into weekly surveillance activities within the CDB. Given the large proportion of newly acquired infections identified in the prison population, this data may be used by PHUs and the State Department of Health to engage correctional centres in further studies and in the development of treatment programs for prisoners, a priority population in state[28] and national strategies.[29]

The system can also potentially identify non-IDU-related HCV infections, though only if they have undergone previous HCV testing or have acutely elevated ALT test results through Pathology Queensland. The inability to efficiently access both interstate and private HCV laboratory testing data limits the usefulness of this system in its ability to detect all newly acquired cases, and therefore cases of non-IDU-related HCV infection. However, where cases of non-IDU-related HCV infection are not detected by the system, individuals or their clinicians are able to alert their local PHU with concerns about potential exposure risks. In such instances, the existence of the current system would demonstrate to the public that the Department of Health conducts routine surveillance to detect such occurrences, and therefore also provides an element of protection from any associated public health risk. Previously, the lack of such a system may have been a point of potential criticism, particularly given Queensland was the only state not to identify or report newly acquired HCV infections.

An additional method to increase system usefulness would be to legislate hepatitis C as a notifiable condition upon laboratory testing. As negative anti-

HCV antibody test results would be automatically notified, such legislation, similar to that in British Columbia, Canada,[30] would provide efficient access to all negative hepatitis C test results, both public and private, through NOCS. This legislative change would result in increased case ascertainment and overall usefulness of the system. However, such a legislative change may lead to privacy concerns among the community and lead to a decreased willingness to undergo hepatitis C testing, potentially leading to significant harms from undiagnosed hepatitis C. This type of approach would require significant communication from the State Department of Health that address any concerns and emphasise that any legislative changes are in the public interest.

Another legislative option to improve case ascertainment would be to make newly acquired hepatitis C a 'clinically notifiable condition' in the *Public Health Regulation 2005*.[11] This could potentially increase the number of newly acquired hepatitis C cases notified that have evidence of clinical hepatitis (Box 1), but no negative anti-HCV antibody test results within the previous 24 months. Though clinicians have been historically poor at notifying clinical infectious disease conditions,[31,32] the reporting of any newly acquired cases that would otherwise go undetected might increase the system's usefulness. Even small increases in case ascertainment can result in significant impacts, as a single case of non-IDU-related HCV infection may identify ongoing public health threats, thus enabling a response to prevent further transmission.

Simplicity

The underlying Stata code I developed for the data linkage process is technically complex, and any alterations to the linkage algorithm requires someone familiar with Stata code and data manipulation. However, the benefits of the data linkage process are the accuracy and efficiency in how it operates, and the weekly surveillance activities are simple to perform and require no technical expertise. Performing the data extraction and linkage required little training and the necessary steps were detailed in the Work Instruction (Appendix B). The newly acquired laboratory definitive evidence case definition was easy to apply, whereas the clinical evidence definition requires other causes of acute hepatitis to be excluded. Future evaluations of the system should review the

benefits of using the clinical evidence case definition, with regards to increased case ascertainment, against the added complexity and resources required to include this aspect of the system. Evaluations of the system could also include exploring improved systematic identification of other causes of acute hepatitis, such as through the inclusion of hepatitis B serology, hepatitis A serology, and aspartate aminotransferase levels in the AUSLAB data extract.

Flexibility

There were no new demands or changes to information needs during the implementation of this system. However, the fields reported to the NNDSS for newly acquired hepatitis C are currently under review, with the potential addition and removal of some fields (Appendix A). Adapting to these changes would require that the relevant information is collected, either through the diagnosing clinician surveillance form or the enhanced surveillance case report form, or both. Changes would also be required to the enhanced surveillance fields in NOCS and how these fields are reported electronically to the NNDSS. These changes could be incorporated into the current system in a timely manner.

The addition of a new national classification for hepatitis C notifications—reinfection—was also being reviewed during the establishment of this system. At the time of writing, a case definition for reinfection had not been determined, though it would likely involve evidence of HCV clearance through negative HCV nucleic acid testing. A separate system would need to be implemented to identify cases of HCV reinfection. As the current system only test results from the public pathology laboratory, a new system to identify HCV reinfection would possess this same limitation. In order to differentiate between reinfection after spontaneous clearance or after treatment, additional information would also need to be gathered from treating clinicians or prescribing data from the Pharmaceutical Benefits Scheme.

Data quality

Matching new hepatitis C notifications with previous HCV antibody and ALT test results provided an accurate method to identify notifications meeting components of the newly acquired case definition. Manual review of identifying information in NOCS and AUSLAB by the Data Services Team for matches provided a quality assurance process to assess the likelihood of a true match, and successfully identified false positive matches that did occur. This process was particularly important for cases where the notification or testing data had been anonymity coded.

Imprisonment, either at the time of diagnosis or within the previous 24 months, is able to be accurately and systematically captured for all identified cases of newly acquired infection through patient location recorded in NOCS and AUSLAB data extracts. Additional risk factor data were collected through the diagnosing clinician surveillance form and enhanced surveillance CRF, though the quality of these data is dependent on both the case information available to the clinician, and the information disclosed by the case. Additionally, cases identified as newly acquired through acutely elevated ALT levels may have other reasons for acute hepatitis that are unknown to the diagnosing clinician, and not a result of acute HCV infection. As mentioned, the use of the clinical evidence case definition in the system should be explored in future evaluations.

Acceptability

The data linkage process was developed with the aim of being sustainable and incorporated into weekly notifications reporting. This was successfully achieved, with the data extraction and linkage taking fewer than 30 minutes to complete as part of the weekly notification process. The relatively small number of diagnosing clinician surveillance forms to be faxed on a weekly basis (<6) also meant that minimal resources were required from the Data Services Team to perform this task.

The relatively high response rate (79%) of diagnosing clinicians completing the surveillance form is an indicator that this task was largely acceptable among this

group. The engagement process with general practitioners in developing the form was likely a key contributing factor in achieving this outcome. This process assisted us in ensuring the significance of the form was clear, and that the form was able to be completed accurately and efficiently.

The acceptability of the system to PHU staff is difficult to determine at this stage, as at 30 June 2017, only six cases had required follow-up during 2017, which was completed using the updated CRF. Future evaluations of the system should involve a formal assessment of PHU follow-up processes.

Sensitivity

By matching hepatitis C notifications from 2011 to 2016 with previous HCV testing data, the system identified 12% of all hepatitis C notifications as newly acquired infections. As previously mentioned, given the lack of previous private laboratory testing data, this is an underestimate of the true number of newly acquired HCV infections. An additional consideration is that the high proportion of both asymptomatic and non-specific illnesses during the acute phase of infection will result in an undercount of hepatitis C notifications. Quantifying the sensitivity of the system to identify newly acquired HCV infections is not possible as the true number of HCV infections that were acquired in the preceding 24 months before diagnosis is unknown. However, comparison of the proportion of all hepatitis C notifications reported as newly acquired with other states and territories allows for an estimate of the relative sensitivity of the system. This proportion for Queensland was the second highest in Australia from 2011 to 2016, and the highest in 2016. The use of public laboratory services for correctional centres in Queensland and Western Australia, and the availability of these data, likely contributed to the high proportions of newly acquired infections identified in these two states.

As previously discussed, the ability to systematically access private laboratory HCV testing data would improve the identification of newly acquired cases, though would require legislative changes that require provision of negative testing data for surveillance purposes. While manually reviewing individual private laboratory testing data is possible within the CDB, the extra resources

required to undertake this task meant that it was not pursued. Future improvements of the system could consider scoping possible methods to efficiently access and use private laboratory testing data for improved identification of newly acquired HCV infections.

The sensitivity of the system to detect non-IDU-related cases or clusters is influenced by the total number of cases identified as newly acquired, and the ability of the diagnosing clinician surveillance form and PHU follow-up to identify these cases. Due to the asymptomatic nature of HCV infection, clusters of related cases may be spread over time. Additionally, cases that belong to a cluster would only be followed up if they meet the newly acquired case definition. The ability of the system to identify an epidemiological link between cases in a cluster is likely to be limited, and relies on enhanced surveillance. The most likely scenario in which a cluster of non-IDU-related HCV transmission is identified would occur after PHU follow-up of a single case without traditional risk factors for HCV transmission, subsequently triggering a public health investigation and response. The hepatitis C CDNA Series of National Guidelines for Public Health Units provides information for PHUs to assist with exposure investigations and management of a potential cluster of cases.[33]

Faxing surveillance forms to a selected proportion of clinicians who diagnose new notifications of unspecified disease could potentially improve case ascertainment, through would require extra resources. For instance, a 30% sample of unspecified cases not imprisoned at the time of diagnosis would result in an additional 12 faxes per week. A trial of this method could be considered and evaluated in future system reviews.

Predictive value positive

The matching and non-matching weights applied in the linkage algorithm (Box 4) were developed to provide a high predictive value positive, which was achieved, with over 99% of matches representing true matches. This aspect of the system improved its acceptability to users performing the linkage and entering data, as less time was required to manually review identifying information and remove false-positive matches as part of weekly surveillance

processes. The false positive matches that occurred, due to individuals with similar names and same date of birth, were unavoidable due to the process of probabilistic matching. Changes to the matching algorithm to avoid the occasional false positive matches would decrease the sensitivity of the system and overall case ascertainment.

Representativeness

The sole use of previous public pathology laboratory testing to identify newly acquired cases creates a potential selection bias towards those more likely to use public pathology services. As demonstrated in the results, newly acquired cases were more commonly male, aged younger than 30 years, and imprisoned at the time of diagnosis when compared to unspecified cases. These differences may be due to a lack of representativeness or may reflect true differences in the characteristics of individuals who have acquired their disease in the 24 months before diagnosis. Previous studies have estimated an age at first drug injection in Australia of 18–19 years,[34,35] with a mean time from first injection to HCV seroconversion of 4.4 years.[34] Additionally, those attending Needle and Syringe Programs who have been imprisoned in the preceding year have higher HCV antibody prevalence than those who have not been incarcerated.[35] This evidence suggests that the demographic characteristics of newly acquired cases identified by our system are likely to be representative of individuals who have truly acquired their HCV infection within the previous 24 months. As previously discussed, representativeness of those identified with newly acquired infections could be improved through clinical notification of acute hepatitis C and accessing previous private laboratory testing data.

Timeliness

Due to the high proportion of asymptomatic acute HCV infections and the 10–14 week incubation period for those who do develop acute hepatitis, the ability of any surveillance system to detect clustering of HCV infections in a timely manner is limited. As the data linkage occurs on a weekly basis, and diagnosing clinicians are advised to return the diagnosing clinician surveillance form within 14 days, the time from initial hepatitis C notification to the return of the

surveillance form may be up to 3 weeks. In cases of potential non-IDU-related HCV infection, PHU follow-up should identify potential transmission routes that require further investigation. In some instances, such as 'tampering' with injectable substances in a nosocomial setting,[9] there may be an ongoing risk to public health that requires a timely response to prevent further HCV transmission. However, in the context of the natural history of the disease, the time taken for data linkage and gathering of risk factor data is likely to be small in comparison to the overall time period the public health threat has existed.

Stability

The weekly surveillance activities require Stata 14 and extended user access to AUSLAB in order to perform the data extraction and linkage processes. In the event of leave or illness among staff members who usually perform the linkage process, the Work Instruction developed provides other staff with the steps required to perform these tasks. Back-ups of the Stata .do file used to perform the linkage were maintained to provide an extra measure of stability. Increased competency in Stata code writing among Epidemiology and Research Unit team members would improve system stability to ensure the system is able to continue to operate in the event of unforeseen system failures

Conclusions

Surveillance of newly acquired hepatitis C infections is an important public health measure to monitor HCV transmission trends and evaluate public health interventions. The challenges related to hepatitis C surveillance—high case burden, asymptomatic infections, and frequent use of anonymity coded testing—made data linkage a suitable and efficient method to identify newly acquired infections in Queensland. The established surveillance system identified relatively high numbers of newly acquired infections compared to other states and territories, while only using previous public pathology test results, and therefore represents an underestimate of the true number of newly acquired HCV infections. This highlights the importance of access to negative pathology test results, both public and private, for certain diseases where monitoring of previous negative testing is a key component of its surveillance.

References

1. The Kirby Institute. *HIV, viral hepatitis and sexually transmissible infections in Australia: annual surveillance report 2016*. [Internet]. Sydney (AUST): The Kirby Institute, UNSW; 2016 [cited 2017 Sept 21]. Available from: https://kirby.unsw.edu.au/report/annual-surveillance-report-hiv-viral-hepatitis-stis-2016

2. Robotin MC, Copland J, Tallis G, Coleman D, Giele C, Carter L, et al. Surveillance for newly acquired hepatitis C in Australia. *J Gastroenterol Hepatol* 2004;19(3):283-8.

3. Micallef J, Kaldor J, Dore G. Spontaneous viral clearance following acute hepatitis C infection: a systematic review of longitudinal studies. *J Viral Hepat* 2006;13(1):34-41.

4. Kohli A, Shaffer A, Sherman A, Kottilil S. Treatment of hepatitis C: a systematic review. *JAMA* 2014;312(6):631-40.

5. Maheshwari A, Ray S, Thuluvath PJ. Acute hepatitis C. *Lancet* 2008;372(9635):321-32.

6. Kamal SM. Acute hepatitis C: a systematic review. *Am J Gastroenterol* 2008;103(5):1283-97.

7. Department of Health, Victoria. *Hepatitis C lookback - Information update - October 2010* [Internet]. Melbourne (AUST): State Government of Victoria; 2010 [cited 2017 Mar 29]. Available from: https://www2.health.vic.gov.au/about/publications/researchandreports/Hepatitis%20C%20lookback%20-%20Information%20update%20-%20October%202010

8. Department of Health, Victoria. *Public health hepatitis C lookback completed* [Internet]. Melbourne (AUST): State Government of Victoria; 2011 [cited 2017 Mar 29]. Available from: https://hnb.dhs.vic.gov.au/web/pubaff/medrel.nsf/LinkView/CC55E09E295D6504CA2578920015B730?OpenDocument

9. Hatia RI, Dimitrova Z, Skums P, Teo EY-L, Teo C-G. Nosocomial hepatitis C virus transmission from tampering with injectable anesthetic opioids. *Hepatology* 2015;62(1):101-10.

10. Communicable Diseases Network Australia. *Hepatitis C (newly acquired) case definition* Canberra (AUST): Australian Government Department of Health; 2015 [cited 2016 Oct 20]. Available from: http://www.health.gov.au/internet/main/publishing.nsf/Content/cda-surveil-nndss-casedefs-cd_hepcnew.htm

11. Queensland Government. *Public Health Regulation 2005* [Internet]. Brisbane (AUST): Queensland Government; 2016 [cited 2016 Jul 27]. Available from: https://www.legislation.qld.gov.au/LEGISLTN/CURRENT/P/PubHealR05.pdf

12. Queensland Government. *Public Health Act 2005* [Internet]. Brisbane (AUST): Queensland Governement; 2017 [cited 2017 May 2]. Available from: https://www.legislation.qld.gov.au/LEGISLTN/CURRENT/P/PubHealA05.pdf

13. Higgins N, Fielding J. The effectiveness of intensive laboratory follow-up for hepatitis C infections in Victoria, January-March 2006. *Vic Infect Dis Bull* 2006;9(3):58-62.

14. Staff MP, Brnabic AJ, Schwarz J, Holt DA. Public health surveillance of hepatitis C: can it identify incident cases? *Aust N Z J Public Health* 2000;24(2):198-200.

15. Bateman-Steel C, Smedley E, Kong M, Ferson M. Hepatitis C enhanced surveillance: results from a southeastern Sydney pilot program. *Public Health Res Pract* 2015;25(2):e2521520.

16. Tobin S. Hepatitis C: enhancing routine surveillance in Victoria. *Vic Infect Dis Bull* 2001;4(2):17-9.

17. Guy R, Devadason D, Lim M, Higgins N, Pedrana A, Gibson K, et al. Enhanced case detection for newly acquired hepatitis C infection: epidemiological findings and health service implications. *Commun Dis Intell Q Rep* 2008;32(2):250.

18. Walsh N, Lim M, Hellard M. Using a surveillance system to identify and treat newly acquired hepatitis C infection. *J Gastroenterol Hepatol* 2008;23(12):1891-4.

19. State Government of Victoria. *Public Health and Wellbeing Act 2008* [Internet]. Melbourne (AUST): State Government of Victoria; 2017 [cited 2017 May 3]. Available from: http://www.legislation.vic.gov.au/

20. Department of Health & Human Services, State Government of Victoria. *Notification of hepatitis C* [Internet]. Melbourne (AUST): State Government of Victoria; 2016 [cited 2016 Oct 20]. Available from: https://www2.health.vic.gov.au/about/publications/formsandtemplates/notification-of-hepatitis-c

21. Chung RT. Acute hepatitis C virus infection. *Clin Infect Dis* 2005;41(S1):S14-7.

22. Mondelli MU, Cerino A, Cividini A. Acute hepatitis C: diagnosis and management. *J Hepatol* 2005;42(1):S108-14.

23. Blasnick M. *Help for reclink* [Internet]. Boston (USA): Boston College; 2010 [cited 2016 Nov 3]. Available from: http://fmwww.bc.edu/RePEc/bocode/r/reclink.html

24. Australian Government Department of Health. *National Notifiable Diseases Surveillance System data* [Internet]. Canberra (AUST): Australian Government Department of Health; 2017 [cited 2017 Apr 18]. Available from: http://www9.health.gov.au/cda/source/cda-index.cfm

25. Australian Bureau of Statistics. *3101.0 - Australian Demographic Statistics, Sep 2016: Table 4. Estimated Resident Population, States and Territories (Number)* [Internet]. Canberra (AUST): Australian Bureau of

Statistics; 2017 [updated 2017 Mar 23; cited 2017 Apr 19]. Available from: http://www.abs.gov.au/AUSSTATS/abs@.nsf/DetailsPage/3101.0Sep%202016?OpenDocument

26. German RR, Lee L, Horan J, Milstein R, Pertowski C, Waller M. Updated guidelines for evaluating public health surveillance systems. *MMWR Recomm Rep* 2001;50(1-35).

27. Australian Bureau of Statistics. *4517.0 - Prisoners in Australia, 2016: Prisoner characteristics, states and territories (Tables 13 to 34)* [Internet]. Canberra (AUST): Australian Bureau of Statistics; 2016 [cited 2017 May 25]. Available from: http://www.abs.gov.au/AUSSTATS/abs@.nsf/DetailsPage/4517.02016?OpenDocument

28. Queensland Health. *Queensland Hepatitis C Action Plan 2016–2021*. Brisbane (AUST): Queensland Health; 2016.

29. Australian Government Department of Health. *Fourth National Hepatitis C Strategy 2014–2017*. Canberra (AUST): Commonwealth of Australia; 2014.

30. British Columbia Government. *Public Health Act* [Internet]. Victoria (CAN): British Columbia Government; 2008 [updated 27 July 2017; cited 2017 Aug 1]. Available from: http://www.bclaws.ca/civix/document/id/complete/statreg/08028_01

31. Allen CJ, Ferson MJ. Notification of infectious diseases by general practitioners: a quantitative and qualitative study. *Med J Aust* 2000;172(7):325-8.

32. Blogg S, Trent M. Doctors' notifications of pertussis. *NSW Public Health Bull* 1998;9(4):53-4.

33. Communicable Diseases Network Australia. *Hepatitis C: CDNA Series of National Guidelines for Public Health Units* [Internet]. Canberra

(AUST): Australian Government Department of Health; 2015 [cited 2018 Feb 10]. Available from: http://www.health.gov.au/internet/main/publishing.nsf/Content/cdna-song-hepc.htm

34. Maher L, Jalaludin B, Chant KG, Jayasuriya R, Sladden T, Kaldor JM, et al. Incidence and risk factors for hepatitis C seroconversion in injecting drug users in Australia. *Addiction* 2006;101(10):1499-508.

35. Memedovic S, Iversen J, Geddes L, Maher L. *Australian Needle Syringe Program Survey National Data Report 2012–2016: prevalence of HIV, HCV and injecting and sexual behaviour among NSP attendees*. Sydney (AUST): Kirby Institute, UNSW; 2017.

Appendix A—Hepatitis C enhanced surveillance fields

Injecting drug use	
Injecting drug use in the previous 2 years	Never injected drugs
Injecting drug use but not in the previous 2 years	Injecting drug use unknown
Other risk factors	
Blood/blood products/tissues in Australia	Imprisonment
Blood/blood products/tissues overseas	Health care worker with no documented exposure
Haemodialysis	Household contact with HCV
Occupational needlestick/biohazardous injury in healthcare worker	Non-IDU remote risk (non-IDU associated risk identified, but not in the 24 months prior to diagnosis)
Occupational needlestick/biohazardous injury in non-healthcare worker	Other risk within the 24 months prior to diagnosis
Surgical work	Risk unable to be determined
Major dental surgery	Unknown (not recorded)
Tattoos	Organ transplantation in Australia
Acupuncture	Organ transplantation overseas
Ear or body piercing	Non-occupational or unspecified needlestick/biohazardous injury
Perinatal transmission	Sexual partner of same sex with HCV
Sexual partner of opposite sex with HCV	
Reason for testing	
Investigation of symptomatic hepatitis	Occupational exposure (exposed)
Abnormal liver function test (not symptomatic)	Perioperative
Blood or organ donor screen	Patient request
Prison screen	Research or study
Antenatal screen	Other
Drug/alcohol screen	Unknown (not recorded)
STI screen	

Appendix B—Hepatitis C work instruction

Hepatitis C (Newly Acquired) Surveillance Instructions

• PURPOSE

• To fulfill reporting requirements of hepatitis C (newly acquired) notifications to the National Notifiable Diseases Surveillance System

Work Instruction file location: U:\CDU\EPI\DisGP\BBVSTI\HepC\Newly acquired Hep C

Link to AUSLAB extended enquiry manual:
http://qis.health.qld.gov.au/DocumentManagement/Default.aspx?DocumentID=21592

• REQUIREMENTS

SQL developer
AUSLAB Restricted Access (particularly on Extended Enquiries)
Stata 14 (with 'reclink' and 'egenmore' packages installed)
Microsoft Excel
Access to file paths: U:\CDU\EPI\DisGP\BBVSTI\HepC\Newly acquired Hep C
NOCS Access (State-wide User or higher)

• NOTIFICATION CRITERIA

Hepatitis C (newly acquired)
Reporting: Only confirmed cases should be notified.

Confirmed case

A confirmed case requires either:

1. Laboratory definitive evidence

OR

2. Laboratory suggestive evidence AND clinical evidence.

Laboratory definitive evidence

1. Detection of anti-hepatitis C antibody from a person who has had a negative anti-hepatitis C antibody test recorded within the past 24 months

OR

2. Detection of hepatitis C virus by nucleic acid testing from a person who has a negative anti-hepatitis C antibody test result currently, or has had, within the past 24 months

OR

3. Detection of anti-hepatitis C antibody from a child aged 18 months to 24 months

OR

4. Detection of hepatitis C virus by nucleic acid testing in a child aged 3 months to 24 months.

Laboratory suggestive evidence

Detection of anti-hepatitis C antibody, or hepatitis C virus by nucleic acid testing in a patient with no prior evidence of hepatitis C infection.

Clinical evidence

Clinical hepatitis within the past 24 months (where other causes of acute hepatitis have been excluded) defined as:

1. Jaundice

OR

2. Bilirubin in urine

OR

3. Alanine transaminase (ALT) ten times the upper limit of normal.

Hepatitis C (unspecified)

Reporting: Only confirmed cases should be notified.

Confirmed case

A confirmed case requires laboratory definitive evidence AND that the case does not meet any of the criteria for a newly acquired case AND is aged more than 24 months.

Laboratory definitive evidence

In a person with no prior evidence of hepatitis C virus infection:

1. Detection of anti-hepatitis C antibody

OR

2. Detection of hepatitis C virus by nucleic acid testing.

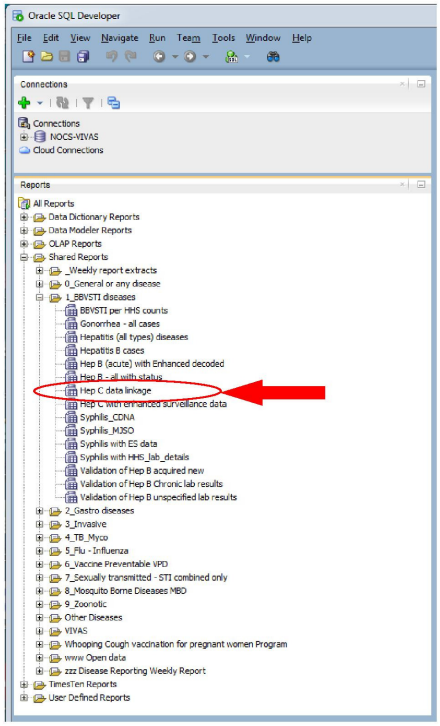
• TASK LIST

- Extraction of hepatitis C notification data from NOCS
- Extraction of hepatitis C testing data from AUSLAB
- Importing and linking NOCS and AUSLAB data in Stata
- Changing appropriate notifications to hepatitis C (newly acquired) in NOCS
- Entering data into the relevant enhanced surveillance fields in NOCS

• PROCESS

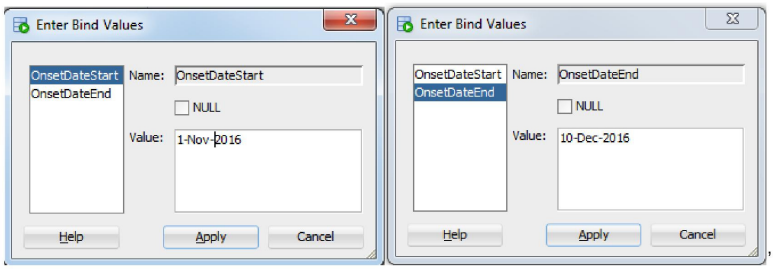
1. Extraction of NOCS hepatitis C Data

1.1. Data downloaded on Monday mornings from SQL DEVELOPER using the pre-set query 'Hep C data linkage' (n.b. extracted date must include year in a 4-digit format)

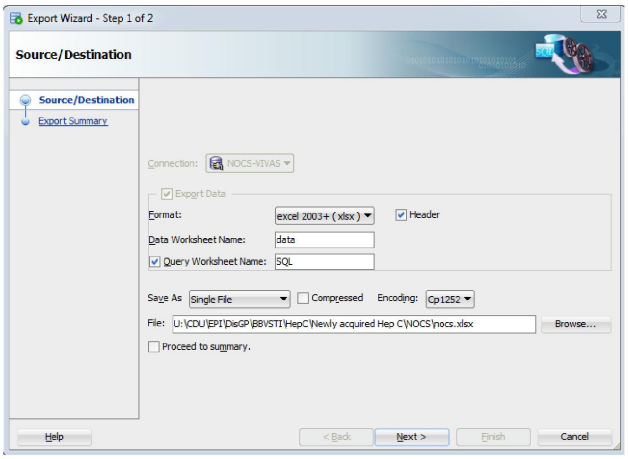


1.2. Click on Reports Tab – Shared Reports > 1_BBVSTI diseases > Hep C data linkage

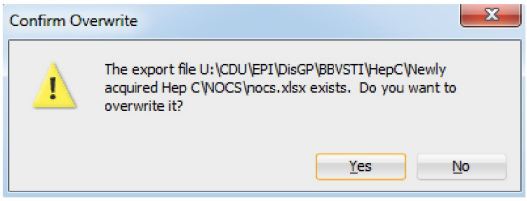
1.3. Select Connection – NOCS-VIVAS > click 'OK'
1.4. Enter Bind values – Change OnsetDateStart = **At least 2 months before current date** > Change NotificationDateEnd = **current date** (use format eg 1-Jan-2017) > click 'Apply



1.5. Right click anywhere in the extract data > Export
1.6. Click on Browse > Navigate to: **U:\CDU\EPI\DisGP\BBVSTI\HepC\Newly acquired Hep C\ NOCS** > File Name: **nocs.xlsx** > Save > Next



1.7. Do you Want to overwrite it > Yes

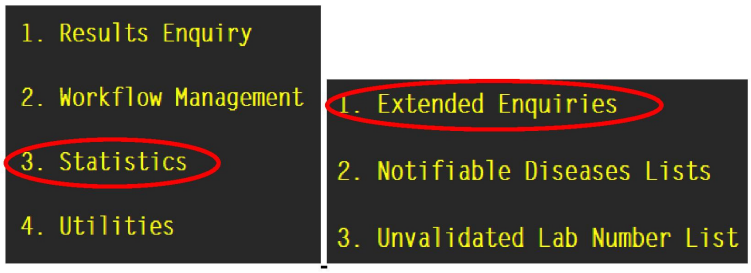


1.8. > Finish
1.9. File will be found in U:\CDU\EPI\DisGP\BBVSTI\HepC\Newly acquired Hep C\NOCS

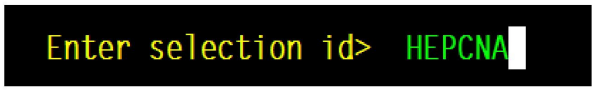
2. Extraction of AUSLAB hepatitis C testing data

2.1. Data extracted Monday mornings through AUSLAB extended enquiry (n.b. the extraction time may be slow if performed before 11:00 am)

2.2. Open AUSLAB > 3. Statistics > 1. Extended enquiries



2.3. **F6** > Enter selection id> **HEPCNA** (n.b. this needs to be entered before the date range is entered any date range is cleared by this step)



2.4. The Result Def1 field (on the second page) will now be populated with the below:

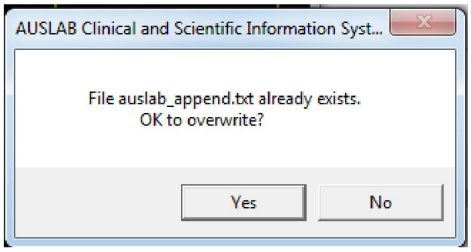
2.5. Date Range = **Current and previous month > Enter**.

Ranges: must be written in following format with square bracket: YYYYM[X-Y]. e.g. 20160[1-2] would provide data for the months of January and February 2016, 20161[0-1] would provided data for the months of October and November 2016. (n.b. cannot use two-digit numbers to define a range in the square bracket).
And statement: uses a " | " statement to separate dates. e.g. 201612 | 201701 would provide data for December 2016 and January 2017. (n.b. spaces surround the '|' character).

2.6. Shift F5 > Enter dump format: **HEPCNA > Enter**

2.7. Enter DOS filename: **auslab_append > Enter** (n.b. do not specify .CSV)

2.8. If there is a previous auslab_append.txt file in C:\AUSLAB, you will be prompted to overwrite the existing file: OK to overwrite > **Yes**



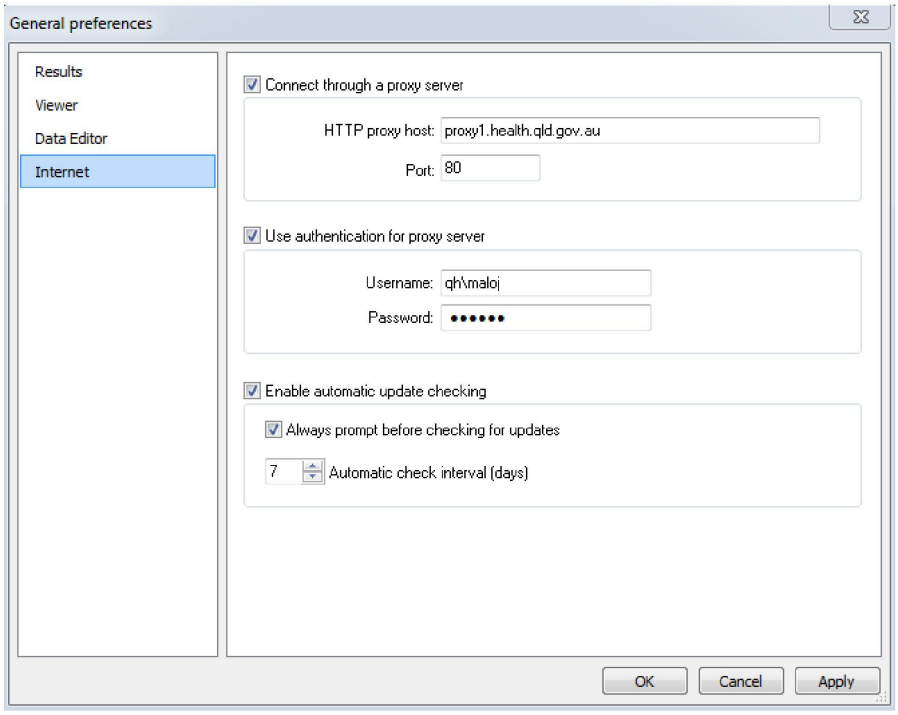
2.9. The file will automatically open in Excel. Click 'X' to close Excel as the file does not need to be saved.

2.10. File is saved to location: C:\AUSLAB

2.11. Time for data extraction will be approximately five minutes, though may take longer for a larger extraction. The white cursor will stop flashing when the file has been saved and the "Enter filename: " command will disappear.

3. Installing 'reclink' and 'egenmore' packages into Stata

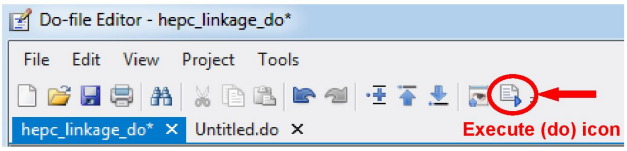
3.1. Skip this step if these packages have been previously installed
3.2. Open Stata
3.3. Ensure connection to a proxy server has been set up.
3.3.1. Edit > Preferences > General Preferences > Internet
- **3.3.1.1.** HTTP proxy host: proxy1.health.qld.gov.au
- **3.3.1.2.** Port: **80**
- **3.3.1.3.** Username: **qh\Novell login** (n.b. preceded by: **qh**)
- **3.3.1.4.** Password: **Novell password** (n.b. requires updating when Novell password is updated)
- **3.3.1.5.** Apply
- **3.3.1.6.** OK



3.3.2. In the Stata command window type: ssc install reclink
3.3.3. In the Stata command window type: ssc install egenmore
3.3.4. Packages will install automatically. This only needs to be performed once.

4. Importing NOCS and AUSLAB data into Stata for linkage

4.1. Open file U:\CDU\EPI\DisGP\BBVSTI\HepC\Newly acquired Hep C\Linked Stata files\hepc_linkage.do



4.2. Run file by clicking the "**Execute (do)**" icon in the top panel (pictured above)
4.3. Cleaning and linkage process will take approximately 10–15 minutes
4.4. Excel file (hepc_newlyacquired_master.xls) with newly acquired cases saved to U:\CDU\EPI\DisGP\BBVSTI\HepC\Newly acquired Hep C\Newly acquired excel files

5. Data entry into NOCS

5.1. Open file U:\CDU\EPI\DisGP\BBVSTI\HepC\Newly acquired Hep C\Newly acquired excel files\hepc_newlyacquired_master.xls and the tab with todays date
5.2. Visually check to ensure ALL cases have been matched correctly, comparing columns "Name (NOCS)" and "Name (AUSLAB)"
5.3. Insert new column between UR Number and Lab Number (will be column N).
5.4. Insert formula to populate field with notes (copy from previous week). See Appendix 1.
5.5. Open NOCS and, using the Notification ID (NID), search for each notification. Then:
- **5.5.1.1.** Change the ICD Description from Hep C (unspecified) to Hep C (newly acquired) (n.b only for cases that have been identified as newly acquired through a previous negative anti-HCV test at this stage)
- **5.5.1.2.** Add in UR number (if not already present)
- **5.5.1.3.** Add communication – copy and paste from column N.
- **5.5.1.4.** Open the New Enhanced Surveillance form
- **5.5.1.5.** In the "Neg Hep C Test in last 2 years" field, enter YES.
- **5.5.1.6.** If the 'Prison at diagnosis' field is 'Yes' or 'No' in the excel spreadsheet, update the 'Imprisoned at diagnosis' field to 'YES' or 'NO'
- **5.5.1.7.** If the "Previous imprisonment" field is 'Yes' in the excel spreadsheet, update the 'Previous imprisonment' field to 'YES'
- **5.5.1.8.** If notification is identified as potentially newly acquired through acutely elevated ALT levels, in the Notification Text write "#ALTDX#". This will ensure the case is not identified in subsequent linkages.
- **5.5.1.9.** Save (F10)
- **5.5.1.10.** Repeat for each notification

5.6. Filter excel spreadsheet by Prison field = NO.
5.7. For cases where there is no Dr information, try to source this information from another source. See Appendix 2. NOTE: If the Dr is at a hospital, try to find the GP data from Viewer.
5.8. Copy and paste the cases into the sheet labelled "mail_merge"
5.9. Save file.
5.10. Email the unfiltered spreadsheet to CDIS-NoCS-Support for data entry of negative test results onto notifications. See appendix 3.

6. Mail Merge

6.1. Review cases where a clinic fax number exists in the mail_merge tab to ensure sufficient information is present. Note: do not send if "Imprisoned at diagnosis" or "Previous imprisonment" is 'Yes'.
6.2. Open the Hep C newly acquired GP Fax template located in U:\CDU\EPI\DisGP\BBVSTI\HepC\Newly acquired Hep C\Newly acquired excel files
6.3. Do you want to continue > Yes
6.4. Mailings > Finish & Merge > Print documents
6.5. Print and fax forms to the associated clinic fax numbers (N.B. Include a 0 when dialling the fax number)
6.6. Record on each Notification, in the Notes, that the GP has been faxed a survey. "[DD/MM/YYYY] survey faxed [USER ID] CDB"
6.7. Place sent faxes, with confirmation message, in the Hep C Survey folder.

7. Survey Management

7.1. Return of Completed Surveys
7.1.1. On Nocs, enter into the notes "[DD/MM/YYYY] survey returned [USER ID] CDB"
7.1.2. For those previously identified as potentially newly acquired through acutely elevated ALT levels, if the completed survey indicates NO—there is not another identified reason for acutely elevated ALT levels, then change the notification to newly acquired. If the survey indicates YES—there is another reason for acutely elevated ALT levels, leave the notification as unspecified.
7.1.3. Hand to the appropriate Epidemiologist for review and decision if further Enhanced Surveillance is required.
7.1.4. If NO → enter Note "[DD/MM/YYYY] No further follow-up required due to {reason} [USER ID] CDB"
7.1.5. If YES → enter Note "[DD/MM/YYYY] Further follow-up required due to {reason} [USER ID] CDB". Epidemiologist to advise Data Officer, who is to then send Enhanced Surveillance form to PHU.

7.2. Surveys Not Returned
7.2.1. After one week, if survey not returned, call the clinic and advise that you are faxing through the survey again for completion.
7.2.2. On Nocs, enter into the notes "[DD/MM/YYYY] survey faxed [USER ID] CDB"
7.2.3. After another week, if survey not returned, call the clinic and enquire why it has not yet been returned. Advise clinic they can tick Unsure and Unknown if are unable to provide any other information. Look up Viewer to see if any further relevant information eg IV Drug Use can be found. Note this and advise Epidemiologist.
7.3. Querying NoCS
7.3.1. Run following SQL to query NoCS and find all follow-up cases

```
select NOTF_ID, NOTIFIABLE_DIS_ICD_CODE,VALIDITY,NOTES
from NC_NOTIFICATIONS
where NOTIFIABLE_DIS_ICD_CODE = 'B17.7'
AND UPPER( NOTES) LIKE '%SURVEY%'
/
```

Appendix 1 – Excel Formula

=CONCATENATE(TEXT(TODAY(),"dd/mm/yyyy")," Updated ICD to Hep C Newly Acquired "," by [USER ID] CDB. Negative test on ",TEXT(L2,"DD/MM/YYYY")," with AUSLAB testID = ",O2)

Appendix 2 – Doctor Data Searching

Staging table SQL

Viewer lookups

Appendix 3 – Entering Negative Test Results onto NOCS

1) Open the notification
2) Go to the "Test Result" tab
3) Scroll to the end, past the last lab test result recorded
4) Enter data from the excel spreadsheet, into the appropriate fields
    a. Lab Name: Pathology Queensland Central Laboratory
    b. Test Type: Serol Igg
    c. NOTE: Do not amend the ONSET DATE. This needs to stay as is, to reflect the positive test result
5) Save (F10)

DOCUMENT HISTORY

Table A shows the high level changes that have been made to each version of this document and who made them:

TABLE A

Version	Issued	Sections	Pages	Modified by	Comments
1	17/01/2017	All	All	Jonathan Malo	Initial Draft
2	9/2/2017	5 & 6	8	Jonathan Malo	Added mail merge instructions
3	11/05/2017	1,2,5 & 6	3–6, 8–10	Jonathan Malo	Added file location, overwrite instructions, and updated data entry, mail merge, and survey entry information provided by Data Services team
4	12/05/2017	2,5 & 6	5,8,9	Jonathan Malo	Added ward field to extract and details about previous imprisonment
5	19/05/2017	2,5, & 7	5,8,9	Jonathan Malo	Removed 'Request' fields from AUSLAB extract in exchange for ResultDef1. Added details relted to potentially newly acquired cases with acutely elevated ALT levels.
6	02/06/2017	2	5 & 6	Jonathan Malo	Added instructions regarding Excel file dump

Appendix C—Diagnosing clinician surveillance form

Queensland Government

FAX MESSAGE
Department of Health
Prevention Division
Communicable Diseases Branch
PO Box 2368, Fortitude Valley BC 4006

TO:	**Name:**	**FROM:**	**Name:**	Mohana Rajmokan
	Organisation:		**Position:**	Senior Epidemiologist
	Fax:		**Phone:**	(07) 3328 9743
	Date:		**Fax:**	**(07) 3328 9434**

CONFIDENTIAL: HEPATITIS C ENHANCED SURVEILLANCE

Name:		**Office use only**	
Date of birth:		**NOCS ID:**	
Sex:		**Notification date:**	

Dear Doctor

You recently diagnosed a patient with hepatitis C virus (HCV) infection that was notified to Queensland Health. Hepatitis C infection is a legally notifiable condition under the *Public Health Regulation 2005*.

Previous laboratory testing has suggested that your patient acquired their infection **within the previous 24 months**. Newly acquired cases of hepatitis C are of public health importance as we are better able to determine the likely route of disease transmission.

As part of national reporting requirements, Queensland Health is now routinely monitoring newly acquired hepatitis C infections in Queensland. As part of this follow-up, we require further information regarding your patient's history and presence of known risk factors for acquiring HCV. This information will be used to improve public health responses related to outbreak detection and interrupting transmission of HCV.

Curative oral treatments for HCV infection are now available to all persons living with hepatitis C. All patients diagnosed with HCV infection are also recommended to undergo HIV testing and have their immune status for hepatitis B verified—receiving appropriate vaccination in cases of non-immunity.

Please complete the attached questionnaire **within 14 days of receipt**. Note that the relevant Public Health Unit may be in contact with you if further information is required.

Please complete the questions on the following page about the case and return to the Communicable Diseases Unit by fax (07) 3328 9434 or email CDIS-NOCS-SUPPORT@health.qld.gov.au.

If you have any questions about this process, please contact the Communicable Diseases Branch on (07) 3328 9743. Thank you for your assistance.

Dr Stephen Lambert
Medical Director, Epidemiology & Research
Communicable Diseases Branch, Queensland Health

Queensland Government

FAX MESSAGE
Department of Health
Prevention Division
Communicable Diseases Branch
PO Box 2368, Fortitude Valley BC 4006

Name:		**Office use only**	
Date of birth:		**NOCS ID:**	
Sex:		**Notification date:**	

1. Reason for hepatitis C testing (tick the single most accurate response):

- ☐ Investigation of symptomatic hepatitis
- ☐ Abnormal liver function test (asymptomatic)
- ☐ Patient request
- ☐ Occupational exposure
- ☐ Screening (specify type below)
  - ☐ Blood/organ donor ☐ Sexual Health ☐ Antenatal ☐ Drug/alcohol ☐ Refugee ☐ Healthcare worker
- ☐ Other reason:_____
- ☐ Unknown

2. In the past 24 months, has the patient had any of the following exposures (tick all that apply):
If unable to contact patient or information regarding exposures is not available in the patient's clinical history, please tick 'Unsure' for all responses and return the completed form.

Injecting drug use	☐ Yes ☐ No ☐ Unsure
Imprisonment	☐ Yes ☐ No ☐ Unsure
Sexual partner of opposite sex with HCV	☐ Yes ☐ No ☐ Unsure
Sexual partner of same sex with HCV	☐ Yes ☐ No ☐ Unsure
Household contact with HCV	☐ Yes ☐ No ☐ Unsure
Tattoo	☐ Yes ☐ No ☐ Unsure
Ear or body piercing	☐ Yes ☐ No ☐ Unsure
Surgical procedure	☐ Yes ☐ No ☐ Unsure
Dental procedure	☐ Yes ☐ No ☐ Unsure
Received blood/blood products/tissus	☐ Yes ☐ No ☐ Unsure
Organ transplantation	☐ Yes ☐ No ☐ Unsure

Please provide any comments that might be relevant to the patient's likely source of HCV infection:

_____

_____

Name of person completing form:_____Date ___/___/___

Please return the completed form to the Communicable Diseases Branch.
Fax: (07) 3328 9434.
Email: CDIS-NOCS-SUPPORT@health.qld.gov.au

Appendix D—Hepatitis C case report form

Case name: ..... DOB ...../...../..... Notification ID: .....
First name Surname

Hepatitis C (Newly Acquired) Case Report Form

Queensland Government

Public Health Unit Outbreak ID: .....

Completed by: ..... Date sent to NOCS: ...../...../.....

NOTIFICATION: Date PHU notified: ...../...../..... Date initial response: ...../...../.....

Notifier: ..... Organisation: .....

Telephone: ..... Fax: ..... Email: .....

Treating Dr: .....

Telephone: ..... Fax: ..... Email: .....

CASE DETAILS: **UR No:** .....

Name: .....
First name Surname

Date of birth: ...../...../..... Age: ..... Years ..... Months Country of birth: ..... Sex: ☐ Male ☐ Female

☐ Aboriginal ☐ Torres Strait Islander ☐ Aboriginal & Torres Strait Islander ☐ Non-Indigenous ☐ Unknown

English preferred language: ☐ Yes ☐ No – *specify* ..... Ethnicity – *specify* .....

Permanent address: ..... Postcode: .....

Home telephone: ..... Mobile: ..... Email: .....

Occupation: ..... Work telephone: .....

Temporary address (if different from permanent address) .....

Mobile: ..... Email: .....

General Practitioner: Dr .....

Address: ..... Postcode: .....

Telephone: ..... Fax: ..... Email: .....

CLINICAL DETAILS:

Reason for testing (tick only one box):

☐ Symptomatic hepatitis Date of onset: ...../...../.....

☐ Abnormal LFT (asymptomatic) Laboratory: ..... Test result: ..... Date: ...../...../.....

☐ Screening – *specify*: ☐ Blood/organ donor ☐ Prison ☐ Antenatal ☐ Drug/alcohol ☐ STI ☐ Refugee ☐ Healthcare Worker

☐ Postnatal screening in a child born to a HCV positive mother

☐ Patient request

☐ Perioperative

☐ Research/study

☐ Occupational exposure

☐ Other – *specify* .....

Hospitalised: ☐ Yes ☐ No ☐ Unknown Hospital: ..... Date: ...../...../..... to ...../...../.....

Complications: ☐ Yes – *specify* ..... ☐ No ☐ Unknown

Outcome: ☐ Survived ☐ Died Date of death: ...../...../..... ☐ Died of condition ☐ Unknown

LABORATORY:

Date of last negative anti-HCV antibody test: ...../...../.....

Laboratory of notifying specimen: ..... Collection date of notifying specimen: ...../...../.....

PCR: Date collected ...../...../..... Result: ☐ HCV RNA detected ☐ HCV RNA not detected

Case name: ..... DOB ...../...../..... Notification ID: .....
First name Surname

EXPOSURE PERIOD:

Date: ...../...../..... to Date: ...../...../.....
(Last negative anti-HCV antibody test date – 6 months) (date of onset – 2 weeks)

History of injecting drug use. Has the case:

Ever injected drugs? ☐ Yes ☐ No ☐ Unknown

Injected drugs *in the previous 2 years*? ☐ Yes ☐ No ☐ Unknown

Are any of the following risk factors identified during the exposure period?

Imprisonment: ☐ Yes ☐ No ☐ Unknown

Sexual partner of opposite sex with HCV: ☐ Yes ☐ No ☐ Unknown

Sexual partner of same sex with HCV: ☐ Yes ☐ No ☐ Unknown

Household contact with HCV: ☐ Yes ☐ No ☐ Unknown

Perinatal transmission: ☐ Yes ☐ No ☐ Unknown

Non-occupational or unspecified needlestick injury: ☐ Yes ☐ No ☐ Unknown

Healthcare worker with no documented exposure: ☐ Yes ☐ No ☐ Unknown

Occupational needlestick in healthcare worker: ☐ Yes ☐ No ☐ Unknown

Occupational needlestick in non-healthcare worker: ☐ Yes ☐ No ☐ Unknown

For the following risk factors, if yes, please also supply details of dates and name and location of where the exposure occurred				**Date (approximate)**	**Name and location of business/ hospital/ premises**
Major dental surgery:	☐ Yes	☐ No	☐ Unknown	...../...../.....	.....
Surgical work:	☐ Yes	☐ No	☐ Unknown	...../...../.....	.....
Haemodialysis:	☐ Yes	☐ No	☐ Unknown	...../...../.....	.....
Received blood/blood products/tissues:	☐ Yes	☐ No	☐ Unknown	...../...../.....	.....
Organ transplantation (Australia/overseas):	☐ Yes	☐ No	☐ Unknown	...../...../.....	.....
Tattoos:	☐ Yes	☐ No	☐ Unknown	...../...../.....	.....
Acupuncture:	☐ Yes	☐ No	☐ Unknown	...../...../.....	.....
Ear or body piercing:	☐ Yes	☐ No	☐ Unknown	...../...../.....	.....
Other risk within previous 2 years:	☐ Yes	☐ No	☐ Unknown	...../...../.....	.....

Other risk details: .....

.....

During this time was there contact with confirmed/suspected case(s) ☐ Yes ☐ No ☐ Unknown

Name / NID: ..... Telephone: ..... Contact type: .....

Name / NID: ..... Telephone: ..... Contact type: .....

PLACE ACQUIRED:

☐ Queensland ☐ Other Australian state/territory – *specify* .....

☐ Unknown ☐ Other country – *specify* .....

COMMENTS:

(This page is mostly blank)

(This page is not contributing anything meaningful to the thesis)

IV

Epidemiology of vaccine breakthrough and recurrent invasive pneumococcal disease in Queensland

Table of Contents

Prologue

Streptococcus pneumoniae infection is a major cause of mortality and morbidity worldwide. The most severe manifestation of *S. pneumoniae* infection—invasive pneumococcal disease (IPD)—is known to occur more commonly in young infants, the elderly, and those with medical conditions placing them at elevated risk of disease. In Australia, Aboriginal and Torres Strait Islander people are disproportionately affected by the burden of IPD, with rates up to ten times those in the non-Indigenous population.

Countries where universal vaccination programs using pneumococcal protein-polysaccharide conjugate vaccines (PCVs) have been implemented have experienced substantial declines in the rates of IPD, both among targeted and non-targeted groups due to the effects of herd protection from reduced bacterial carriage in the population. The National Immunisation Program (NIP) currently provides a 3-dose primary course of 13-valent pneumococcal conjugate vaccine to infants at 2, 4, and 6 months of age, while many other countries also provide all children with a booster dose at 12 months of age. Children and adults with medical conditions placing them at increased risk of IPD are also recommended to receive pneumococcal vaccines, depending on their age, previous pneumococcal vaccination history, and nature of the underlying condition.

This chapter consists of a data analysis project and an epidemiological study that I planned and conducted, which highlight important questions related to pneumococcal vaccination policy: (1) do Australian children need a booster dose of PCV at 12 months of age to provide long-term protection against pneumococcal conjugate vaccine serotypes? and (2) does a previous episode of IPD increase the risk of future episodes?

Project role

The dataset used for these projects was obtained through a project proposal by a former Queensland PhD candidate, Dr Sarah Sheridan. I was added to the ethics application, updated the project proposal and ethics application to obtain more recent data, and was provided with the dataset to describe the epidemiology of

breakthrough IPD (i.e. conjugate vaccine-type IPD in fully vaccinated children) in Queensland in order to answer research question 1. During an exploratory analysis of the dataset, I noted a small but not insignificant number of cases of recurrent disease. Upon reviewing the literature on recurrent IPD, it was discovered that only one population-based study had calculated incidence rates to determine the risk of recurrent disease.[1] This finding was important, as a individuals with a previous episode of IPD were not recommended at the time to receive pneumococcal vaccine. Therefore, estimating the risk of recurrent disease was then added as a second study, for which I planned and conducted the analysis. I performed all data cleaning and analysis of the dataset for both studies. Where errors in notification or vaccination records were discovered, I provided this information to the relevant members of the Epidemiology and Research Unit to improve data quality for future reporting and research.

Lessons learned

This project was particularly rewarding in applying statistical methods, in this case, Cox proportional hazards modelling, to a real-world dataset. As there was a significant amount of data cleaning and recoding required in the initial dataset, I also learned the importance of keeping a data cleaning log and clearly annotating Stata .do files so that myself or others can follow the procedures taken in the future. In addition, I presented both pieces of work at national and international conferences; this experience provided me with valuable feedback on both the methods and practical implications of these projects.

Public health impact

I presented the findings of these studies at several meetings and conferences (see below). My supervisor and I also wrote a letter to the Australian Technical Advisory Group on Immunisation (ATAGI) (Appendix A) with our findings of the significantly increased risk of recurrent disease, suggesting those with a previous episode of IPD be included in the list of high-risk groups recommended to receive pneumococcal vaccination in the Pneumococcal disease chapter of the *Australian Immunisation Handbook*. This recommendation is currently under consideration by ATAGI.

The findings in the Queensland dataset also led me to plan national studies of breakthrough and recurrent IPD. Ethics approval and the national dataset have been obtained, though issues with data completeness have not allowed me to undertake analysis as part of my MAE projects, but will still be undertaken in the future. Findings from the national studies will provide additional evidence to inform pneumococcal vaccination policy in Australia.

Communication

I communicated the findings of these two projects through the following:

- Estimating the risk of recurrent invasive pneumococcal disease in Queensland, 2001-2015, NCIRS Biostatistics and Epidemiology Special Interest Group, Westmead, NSW, Australia, 3 August 2016
- Estimating the risk of recurrent invasive pneumococcal disease in Queensland, 2001-2015, MAE reports from the field, Canberra, ACT, Australia, 30 August 2016
- Estimating the risk of recurrent invasive pneumococcal disease in Queensland, 2001-2015, Queensland Regional Gerry Murphy Presentation, Herston, QLD, Australia, 17 August 2016
- Breakthrough cases of invasive pneumococcal disease in Queensland children following the introduction of pneumococcal conjugate vaccines, 2001–2015. Australian Epidemiological Association 23rd Annual Scientific Meeting, Canberra, Australia, 14–16 September 2016
- Estimating the risk of recurrent pneumococcal disease—Queensland, Australia, 2001–2015. 8th Southeast Asia and Western Pacific Bi-Regional TEPHINET conference, Siem Reap, Cambodia, 28 November–02 December 2016
- Estimating the risk of recurrent invasive pneumococcal disease in Queensland, 1997–2015. 15th World Congress on Public Health, Melbourne, Australia, 03–07 April 2017
- Letter to ATAGI recommending the inclusion of those with previous IPD as an at-risk group recommended to receive pneumococcal vaccination in the Australian Immunisation Handbook (Appendix A)

Core MAE requirements addressed

- Analysis of a public health dataset—breakthrough IPD
- Plan and conduct an epidemiological study—recurrent IPD
- Presentation at national and international conferences

Acknowledgements

I gratefully acknowledge the many people who contributed to this project:

- Sarah Sheridan, for her initial work and planning on the project.
- Angela Wakefield, for her assistance in clarifying my questions related to the data and explaining the intricacies of IPD surveillance.
- Robert Ware, for reviewing and verifying my use of Cox proportional hazards modelling.
- Stephen Lambert, for the support and networking to improve the usefulness of this work.

Abstract

Breakthrough IPD

Background: Publicly-funded 7-valent pneumococcal conjugate vaccine (7vPCV) was introduced for all Australian infants at 2, 4, and 6 months of age in 2005 (3+0 schedule), and was replaced by 13vPCV in July 2011. A booster dose is available for Aboriginal and Torres Strait Islander children aged 12–18 months, as well as for children with medical conditions placing them at elevated risk of invasive pneumococcal disease (IPD). We aimed to describe the epidemiology of IPD among Queensland children aged younger than 5 years, with emphasis on cases of breakthrough disease.

Methods: Descriptive analysis of enhanced IPD surveillance data and vaccination records in children aged younger than 5 years, Queensland, 2001–2015. Breakthrough cases were defined as those occurring in a child with 3 or more doses of the PCV (7v or 13v), where a serotype contained in all 3 PCV doses was identified as the infecting serotype.

Results: From 2001 to 2015, 1,165 IPD notifications were reported in Queensland children younger than 5 years, with 658 occurring from 2001 to 2004 and 507 from 2005 to 2015. Forty-three cases of breakthrough IPD occurred from 2006 to 2015, the majority (74%) of which occurred since the replacement of 7vPCV with 13vPCV. Since 2012, over 60% of breakthrough cases were caused by serotype 19A, with serotype 19F (19%) the next most common cause of breakthrough disease. The median age of onset for breakthrough cases was 22.2 months and the time since last pneumococcal conjugate vaccine dose to onset of breakthrough disease ranged from 4.5 to 51.6 months

Conclusions: Universal infant vaccination with pneumococcal conjugate vaccines have led to substantial decreases in IPD rates in Queensland children, but the number of 13PCV breakthrough cases remain a concern. Booster dose

PCV13 scheduling should be considered reduce the burden of breakthrough IPD in this age group.

Recurrent IPD

Background: Previous overseas evidence suggests that individuals with previous invasive pneumococcal disease are at higher risk of future episodes of IPD. Currently, Australian recommendations provide funded pneumococcal vaccination to certain groups with medical conditions at elevated risk of IPD, but those with previous IPD are not included in these recommendations. We sought to estimate the risk of recurrent IPD in Queensland children and adults, and explore the potential benefit in providing pneumococcal vaccination to those with previous IPD.

Methods: A retrospective cohort study of IPD notifications from 1 January 1997 to 31 December 2015, using time-to-event analyses to estimate recurrent IPD rates. Recurrent IPD was defined as any repeat notification in an individual more than 30 days after the collection date of the initial notification. Cases that survived more than 14 days after illness onset contributed person-time at risk of disease from the date of illness onset until date of death or the end of the study period. Primary (first episode) IPD rates were calculated using mid-year resident population estimates.

Results: From 1997 to 2015, there were 6,075 notified cases of IPD reported in 5,955 Queensland residents. Of these, 120 (2.0%) were recurrent episodes that occurred in 102 individuals. The annual rate of primary IPD during the study period was 7.8 per 100,000 and the recurrent IPD rate was 264.4 per 100,000 person-years, 35 times the annual incidence of primary IPD. Forty-eight percent of individuals with recurrent IPD had no risk factor identified at the time of their initial episode. Since 2012, one-third of recurrent episodes were caused by 13vPCV serotypes, and an additional 27% were caused by the additional serotypes contained in 23-valent pneumococcal polysaccharide vaccine.

Conclusions: Individuals with previous IPD are at substantially increased risk of future episodes. More than half of recurrent cases may be prevented through targeted use of pneumococcal vaccines. Those with previous IPD should be recommended and funded for pneumococcal vaccination.

Introduction

Streptococcus pneumoniae is a major cause of bacteraemia, pneumonia, and meningitis worldwide, primarily affecting children[2] and the elderly.[3,4] In 2000, *S. pneumoniae* was estimated to result in over 14 million infections and 800,000 deaths globally in children younger than 5 years of age, though these have likely fallen following increased access to pneumococcal vaccines in low-income countries.[2,5]

Pneumococcal infections are categorised as either invasive or non-invasive disease. Cases of invasive pneumococcal disease (IPD) represent severe infections, primarily bacteraemia, meningitis, and bacteraemic pneumonia, with less common invasive presentations such as septic arthritis and peritonitis also occurring.[2,4] Non-invasive disease manifestations include community-acquired pneumonia (CAP), otitis media, and sinusitis. Over 90 different serotypes of *S. pneumoniae* have been identified, the most common of which have capsular antigens contained in pneumococcal vaccines. Transmission occurs via person-to-person spread through contact with infected respiratory droplets from colonised individuals. The burden of IPD is higher among children, the elderly, those with predisposing medical conditions, and others in specific at-risk categories. Rates of vaccine-type (VT) IPD in Australia have declined substantially since the introduction of universal infant vaccination with pneumococcal protein-polysaccharide conjugate vaccines through the National Immunisation Program (NIP), though rates among Aboriginal and Torres Strait Islander people (Indigenous Australians) remain disproportionately high.[6]

In Australia, four pneumococcal-containing vaccines have been funded through the NIP (Table 1). Vaccination with the 7-valent pneumococcal conjugate vaccine (7vPCV) was initially funded through the NIP in 2001 for Aboriginal and Torres Strait Islander children and those with medical conditions placing them at high-risk of IPD.[7] Universal infant vaccination was subsequently introduced in 2005, providing a 3-dose primary course without a booster dose (3+0) at 2, 4, and 6 months of age. A 7vPCV catch-up program was also funded for children younger than 2 years of age, with the number of doses dependent on the age at first dose. As a result of serotype replacement,[8] a 13vPCV replaced

7vPCV on the NIP in July 2011. Vaccination with a 10vPCV was used in the Northern Territory from 2009 to October 2011, after which it was also replaced with 13vPCV. A national catch-up program was also funded to provide children aged 12–35 months, who had completed a primary course with 7vPCV, with a supplementary dose of 13vPCV from October 2011 to September 2012.[9] A 23-valent pneumococcal polysaccharide vaccine (23vPPV) has been available in Australia since 1999, and is currently recommended and funded for Aboriginal and Torres Strait Islander adults aged 50 years and over, non-Indigenous adults aged 65 years and over, and those with certain medical conditions associated with an increased risk of IPD.[7]

Table 1—Serotypes of *Streptococcus pneumoniae* contained in pneumococcal vaccines

Vaccine	Serotypes included in vaccine
7vPCV (Prevenar®)	4, 6B, 9V, 14, 18C, 19F, 23F
10vPCV (Synflorix®)	1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 23F
13vPCV (Prevenar 13®)	1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F
23vPPV (Pneumovax 23®)	1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, 33F

7v, 7-valent; 10v, 10-valent; 13v, 13-valent; 23v, 23-valent; PCV, pneumococcal conjugate vaccine; PPV, pneumococcal polysaccharide vaccine; VT, vaccine-type.

National vaccination coverage at 12 months of age with 3 doses of pneumococcal conjugate vaccine has remained over 90% since 2007, and most recently estimated at 92.1%.[10] In 2004, prior to the introduction of universal infant vaccination, the notification rate of IPD in Australia was 11.7 per 100,000. The annual notification rate decreased to 8.4 per 100,000 per year in 2011 prior to replacement of 7vPCV with 13vPCV, declining further to 6.9 per 100,000 in 2016.[11] The most recent (2012) annual age-specific notification rates have remained relatively high in adults aged 65 years or more (19.3 per 100,000) and children in the second year of life (15.9 per 100,000).[6] In 2012, the rate of IPD was also disproportionately higher among Indigenous Australians (42.0 per 100,000), particularly in Indigenous children younger than 5 years (37.1 per 100,000).[6] While the greatest decreases in VT-IPD have been observed among age groups targeted for vaccination through the NIP, indirect protection in other age groups has also been observed in Australia[6] and overseas.[12-14]

Pneumococcal vaccination schedules and breakthrough disease

The optimal timing and number of PCV doses to provide as part of a national immunisation program depend on the local epidemiology of IPD, cost, and the age groups in which the burden is greatest.[15] In Australia, the 3+0 schedule was implemented due to previous evidence suggesting similar efficacy against vaccine-type IPD with either a 3- or 4-dose 7vPCV schedule.[7,16] Alternative PCV schedules used overseas include both 2- and 3-dose primary courses with a booster dose (2+1 and 3+1) at 12 months of age.

Immunogenicity studies have demonstrated that a 3-dose primary PCV course results in greater antibody concentrations than a 2-dose primary PCV course at 6 months of age, though this difference disappears by 12 months of age.[17] A booster dose as part of a 2+1 schedule results in greater long-term immunogenicity compared to a 3+0 schedule,[17] but this difference has not been demonstrated in relation to IPD outcomes.[18] Each of the 3- and 4-dose PCV schedules have been effective in reducing VT-IPD, carriage, and in providing indirect protection where they have been implemented; differences in the effectiveness between schedules are therefore likely to be subtle and dependent on the local context.[14,18,19] An increase in the number of PCV serotype IPD cases had been noted in recent years by the Epidemiology and Research Unit within the Communicable Diseases Branch, creating the need for a detailed analysis and exploration of these cases.

Pneumococcal vaccination for at-risk groups and recurrent disease

Pneumococcal vaccination (13vPCV, 23vPPV, or both) is recommended for adults with medical conditions associated with an increased risk of IPD such as functional or anatomical asplenia, immunocompromising conditions, and chronic cardiac and lung diseases. The recommendations for the use of 13vPCV and 23vPPV in this group are dependent on the level of risk associated with the predisposing condition(s). Children with medical conditions associated with an increased risk of IPD are recommended to receive a booster dose of 13vPCV at 12 months of age in addition to the 3-dose primary course (i.e. 3+1 schedule), and a dose of 23vPPV at 4–5 years of age.[7]

Recurrent episodes of IPD have been reported to occur in 2–5% of cases, commonly in those with underlying medical conditions placing them at elevated risk of disease.[1,20-29] However, recurrent IPD also may also occur in immunocompetent individuals with no apparent underlying risk factors for disease.[21,27,30] Evidence from the international literature has demonstrated that after an initial episode of IPD, individuals are at significantly higher risk of further episodes when compared to the general population,[1] typically occurring within 12 months of the initial episode. [1,21]

Despite the elevated risk of recurrent disease, individuals with previous IPD are not included in the recommended list of high-risk groups to receive pneumococcal vaccination in Australia.[7] No estimates of recurrent disease have occurred in the Australian context to quantify the risk in those with a previous episode of IPD. Examining the local risk may be useful in informing pneumococcal vaccination policy regarding this potentially high-risk group.

Aims and objectives

Breakthrough IPD*

In the first part of this study, I set out to describe the epidemiology of IPD in Queensland children aged younger than 5 years by:

- describing the burden of IPD by age and infecting serotype.
- determining the frequency of breakthrough cases of IPD.
- identifying infecting serotypes causing breakthrough disease.
- determining the timing of breakthrough disease in relation to the last pneumococcal vaccination.
- identifying factors associated with breakthrough disease.
- comparing the burden of vaccine-type IPD in children aged younger than 12 months to the burden of breakthrough IPD.

Recurrent IPD

In the second part of this study, I set out to describe the epidemiology of recurrent IPD in Queensland by:

- conducting a retrospective cohort study to estimate the risk of recurrent disease.
- identifying factors associated with recurrent disease.
- identifying the proportion of recurrent episodes that are potentially preventable through pneumococcal vaccination.

* Both 7vPCV (Prevenar®) and 13vPCV (Prevenar 13®) are registered for use as a 3+1 schedule, whereas a 3+0 schedule is used in Australia through the National Immunisation Program. As the vaccination schedule provided is not consistent with licensure, the term 'breakthrough' is therefore used in this study instead of 'vaccine failure' to describe cases of IPD caused by a PCV serotype in fully vaccinated children.

Methods

Case definition and surveillance

IPD has been a notifiable disease in Queensland since 1997 and nationally notifiable since 2001. Queensland reports all cases of IPD to the National Notifiable Diseases Surveillance System (NNDSS). The national IPD case definition requires either the isolation of *S. pneumoniae* from a normally sterile site or the detection of *S. pneumoniae* nucleic acid from a normally sterile site.[31] There is a 30-day reinfection period for IPD notifications, unless the infecting serotype identified in a second specimen is different to that identified in the specimen prompting the first notification. In Queensland, notified cases of IPD are reviewed by the relevant public health unit (PHU) and Communicable Diseases Branch (CDB) epidemiologist responsible for IPD to ensure the case definition is met. Enhanced surveillance occurs for all cases of IPD in children aged younger than 5 years to ascertain risk factors and pneumococcal vaccination history. In IPD cases aged more than 5 years, the CDB epidemiologist also collects enhanced surveillance for many cases (through electronic hospital records), with an improvement in the collection of data in this group over time. Serotyping of *S. pneumoniae* isolates by the state public health reference laboratory, Queensland Forensic and Scientific Services (QFSS), became standard practice in 2001.

Data extraction

Queensland notification records are stored in the Notifiable Conditions System (NOCS) and vaccination records in the Vaccine Information and Administration System (VIVAS). Notifications of IPD with onset dates from 01 January 1997 to 31 December 2015 were extracted from NOCS. Notification records included age, sex, Indigenous status, date of death, clinical category of IPD (bacteraemia, meningitis, pneumonia, other), and any risk factors identified through enhanced surveillance (Table 2). Dates of death were updated with Queensland all-cause death records by the Health Statistics Branch prior to extraction. Records of pneumococcal vaccines (7vPCV, 13vPCV, 23vPPV) received more than 14 days prior to illness onset were considered valid for the purposes of

disease prevention and were extracted from VIVAS. Vaccination records included vaccination date, type, and dose number. In line with the third-dose assumption, where a pneumococcal conjugate vaccine was recorded as the third dose, the first and second doses were assumed to have been received, even in the absence of a record.[32] Overall and age-specific notification rates were calculated using Queensland mid-year estimated resident populations as the denominator.[33] Queensland pneumococcal vaccination coverage data were available from annual and quarterly reports produced by the National Centre for Immunisation Research and Surveillance.[10,34-36]

Table 2—Risk factor fields and definitions collected as part of enhanced surveillance of notified cases of invasive pneumococcal disease

Risk factor field	Definition
Premature	Born less than 37 weeks gestation
Congenital or chromosomal abnormality	Presence of a congenital or chromosomal abnormality
Anatomical or functional asplenia	A history of splenectomy or the presence of a medical condition which results in a non-functioning spleen
Immunocompromised	Presence of an immunocompromising condition or on immunosuppressive therapy at the time of diagnosis
Chronic illness	Presence of a chronic illness
Childcare attendee	Attendance (>4 hrs/week) in a grouped childcare setting outside the home anytime within the 4 weeks prior to diagnosis
Excessive alcohol consumption	Either ≥4 standard drinks/day for females, ≥6 standard drinks/day for males, or alcohol excess noted in medical records with related medical condition and/or hospitalisation
Smoking	Current or ex-smoker
House hold exposure to cigarette smoke	Passive household exposure to cigarette smoke even if person smokes outside only

Time period

Time periods were classified according to the pneumococcal vaccine availability through the NIP: 1997–2000 (pre-7vPCV), 2001–2004 (targeted 7vPCV), 2005–2011 (universal 7vPCV), and 2012–2015 (universal 13vPCV). Due to the 13vPCV catch-up campaign starting in October 2011[9] with relatively low uptake[37] and the July 2011 cohort not completing a 3-dose primary course until January 2012, the universal 13vPCV period was chosen to commence in 2012 to

allow for a transitional period to achieve sufficient population coverage of the six additional serotypes.

Pneumococcal serotypes

Pneumococcal serotypes were grouped according to the pneumococcal vaccine in which they are contained (Table 1), excluding serotypes included in a vaccine of lower valency. Pneumococcal serotypes not contained in any vaccine were considered non-vaccine type (non-VT). Pneumococcal serotypes were defined as unknown/missing if the serotype was recorded as missing, non-typeable, not referred, no isolate, or non-viable. Analysis of infecting serotypes was not performed for cases with illness onset prior to 2001 (pre-7vPCV) as serotyping was not routinely performed during this period. Cases were classified as PCV-type disease if they were caused by a serotype contained in either 7vPCV or 13vPCV at a time when the vaccine was provided through the NIP as part of universal infant vaccination (7vPCV: 2005–2011; 13vPCV: 2012–2015).

Children younger than 5 years of age and breakthrough IPD

Notifications of IPD in children younger than 5 years of age at the time of illness onset from 2001 to 2015 were analysed to describe the burden of disease in this age group. Cases of breakthrough IPD were identified as children younger than 5 years of age who completed a three-dose course of pneumococcal conjugate vaccine (7vPCV and/or 13vPCV) more than 14 days prior to illness onset, where the infecting serotype was contained in all three doses of the vaccination course. Time to last vaccination was defined as the period from the most recent vaccination date of a pneumococcal conjugate vaccine, even if 23vPPV had been received more recently, until the illness onset date. Pearson's chi-squared test of proportions and Fisher's exact test (where expected cell frequency was less than 5) were used to test statistical significance (p-value<0.05).

Recurrent IPD

I conducted a retrospective cohort study to estimate the risk of recurrent IPD in Queensland. Recurrent IPD was defined as any repeat notification in an individual more than 30 days after the collection date of the initial specimen prompting notification, unless a different infecting serotype was identified in an earlier specimen.

For primary IPD, the overall, age-specific, sex-specific, clinical category-specific, and time period-specific rates were calculated using the average estimated mid-year resident population for Queensland over the relevant period as the denominator. Indigenous- and non-Indigenous-specific rates were calculated using the 2006 estimated mid-year resident Indigenous and non-Indigenous populations for Queensland as the denominators.[38]

Time-to-event analyses were performed to estimate the overall and stratified rates of recurrent disease. Cases that survived more than 14 days after illness onset contributed person-time at risk of disease from the date of illness onset until date of death or the end of the study period (31 December 2015). After a recurrent episode of IPD, cases were considered to remain at risk of further recurrence and therefore continued contributing to the person-time denominator.

Univariate and multivariate Cox proportional hazards analyses were performed to determine factors identified at the time of the first episode associated with recurrent disease. Proportional hazards analyses were performed separately for people aged younger than 15 years and those aged 15 years or more due to differences in the surveillance and reporting of age-associated risk factors (e.g. prematurity in children, excessive alcohol consumption in adults). Likelihood ratio tests (LRT) were used to calculate p-values to test the overall significance of variables in univariate and multivariate analyses. Wald tests were used to calculate p-values for individual strata of categorical variables. After univariate analyses, variables with an LRT $p<0.25$ were included in the initial model for multivariate modelling. A backwards selection procedure was used to identify variables that were either significant (LRT $p<0.05$) in the multivariate model or

caused a 10% change or more to the adjusted coefficients to be retained in the final model. Covariates that were non-significant (LRT $p \geq 0.05$) in the multivariate model were removed during the backwards selection process. LRTs were used to test interactions between covariates included in the final model and those with a univariate LRT $p < 0.25$. Where not already included in the final model, age and sex were both assessed separately for potential confounding (≥10% change in adjusted coefficients of covariates), and retained in the model where present.

Proportional hazards assumptions were assessed by examining ln-ln survival plots, plots of Kaplan-Meier observed survival curves against Cox predicted curves, Schoenfeld residual plots, and testing for a zero slope in the log hazard ratio function.

All analyses were performed in Stata IC 14.1 (Stata Corp, USA).

Ethics

Ethics approval was obtained from the Children's Health Queensland Hospital and Health Service HREC (HREC/13/QRCH/130) and The Australian National University HREC (Protocol number 2016/252). Access to data was gained through a *Public Health Act 2005* application (approval RD004802).

Results

IPD in children younger than 5 years

From 2001 to 2015, 1,165 IPD notifications were reported in Queensland children younger than 5 years, representing 24% of all IPD notifications during this period. Of these, 18 (2%) had IPD reported as a cause of death. The annual under-5 notification rate was highest in 2001 (73.4 per 100,000), decreasing by 87% to 9.7 per 100,000 by 2015 (Figure 1). The greatest annual decrease in the under-5 notification rate occurred from 2004 to 2005 (-64%), after the introduction of universal infant vaccination with 7vPCV.

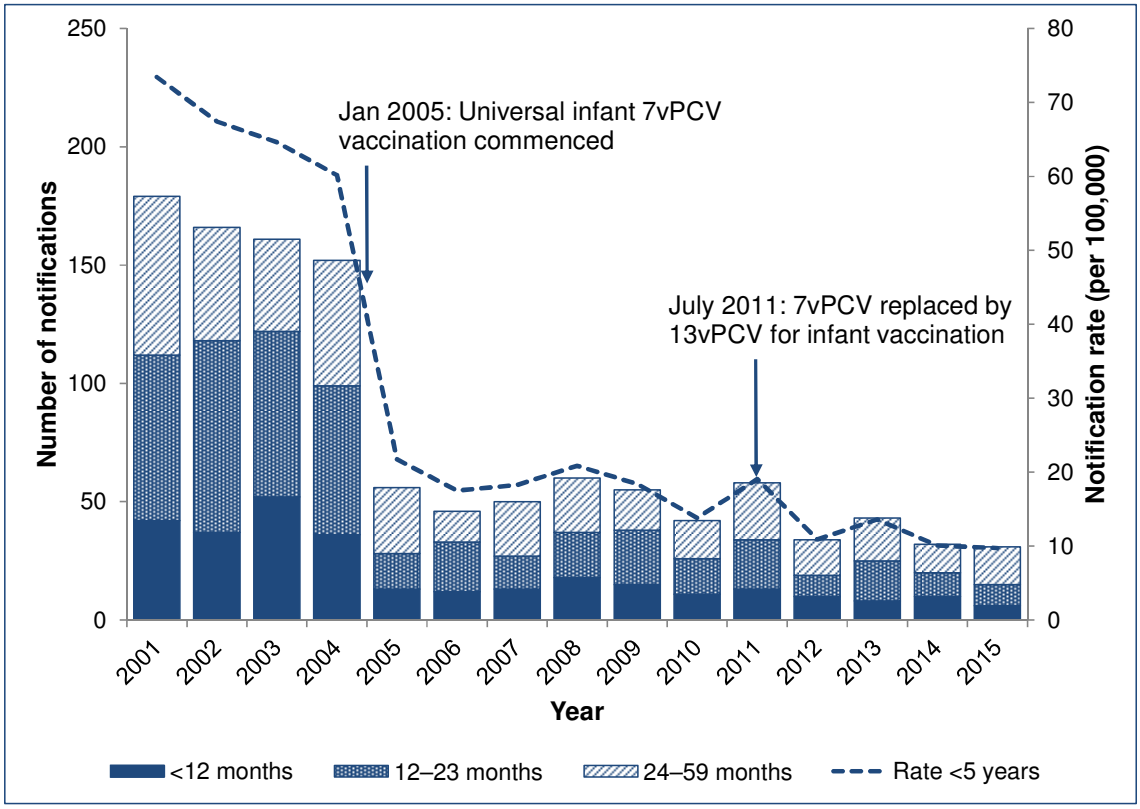


Figure 1—Crude notification counts and annual rates of invasive pneumococcal disease in children aged <5 years, Queensland, 2001–2015. 7vPCV, 7-valent pneumococcal conjugate vaccine; 13vPCV, 13-valent pneumococcal conjugate vaccine.

Notification rates were generally highest in those aged 12–23 months during the study period (Figure 2). Queensland vaccination coverage with three doses of pneumococcal conjugate vaccine (7vPCV or 13PCV) at 12 months of age has steadily increased since introduction, reaching 92.4% in 2015, and rising to over 93% in 2016.

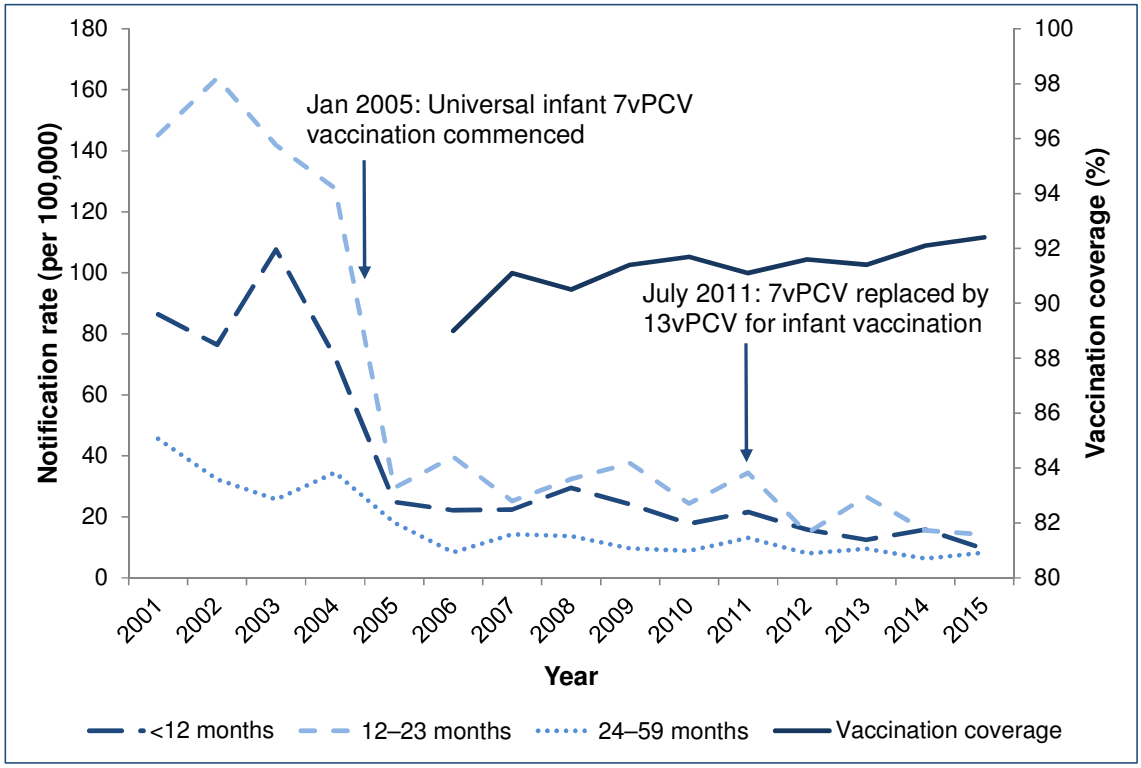


Figure 2—Annual notification rates of invasive pneumococcal disease by age group and 3-dose pneumococcal conjugate vaccine coverage at 12 months of age,[10,34,35] children aged younger than 5 years, Queensland, 2001–2015

Children aged 12–23 months accounted for 39% of notifications in children younger than 5 years of age during the study period (Table 3). From 2012 to 2015, 46% of IPD notifications were caused by serotypes contained in 13vPCV, with an additional 19% caused by additional serotypes contained in 23vPPV. Bacteraemia and bacteraemic pneumonia were the most common clinical presentations of IPD reported.

Table 3—Characteristics of notified cases of invasive pneumococcal disease in children younger than 5 years of age by pneumococcal vaccine program period, Queensland, 2001–2015

	Targeted 7vPCV (2001–2004)		Universal 7vPCV (2005–2011)		Universal 13vPCV (2012–2015)		Total	
	n=658	(%)	n=367	(%)	n=140	(%)	n=1,165	(%)
Age (months)								
<12	167	(25.4)	95	(25.9)	34	(24.3)	296	(25.4)
12–23	284	(43.2)	128	(34.9)	45	(32.1)	457	(39.2)
24–59	207	(31.5)	144	(39.2)	61	(43.6)	412	(35.4)
Sex								
Male	376	(57.1)	221	(60.2)	85	(60.7)	682	(58.5)
Female	282	(42.9)	146	(39.8)	55	(39.3)	483	(41.5)
Indigenous status								
Indigenous	59	(9.0)	56	(15.3)	26	(18.6)	141	(12.1)
Non-Indigenous	564	(85.7)	307	(83.7)	113	(80.7)	984	(84.5)
Unknown	35	(5.3)	4	(1.1)	1	(0.7)	40	(3.4)
Death due to IPD								
Yes	4	(0.6)	10	(2.7)	4	(2.9)	18	(1.5)
No/unknown	654	(99.4)	357	(97.3)	136	(97.1)	1,147	(98.5)
Infecting serotype*								
7vPCV	536	(81.5)	71	(19.3)	15	(10.7)	622	(53.4)
13vPCV	67	(10.2)	193	(52.6)	49	(35.0)	309	(26.5)
23vPPV	16	(2.4)	32	(8.7)	27	(19.3)	75	(6.4)
Non-VT	15	(2.3)	48	(13.1)	39	(27.9)	102	(8.8)
Unknown	24	(3.6)	23	(6.3)	10	(7.1)	57	(4.9)
Clinical syndrome								
Bacteraemia	356	(54.1)	144	(39.2)	53	(37.9)	553	(47.5)
Meningitis	39	(5.9)	37	(10.1)	12	(8.6)	88	(7.6)
Pneumonia	140	(21.3)	142	(38.7)	55	(39.3)	337	(28.9)
Pneumonia & meningitis	4	(0.6)	3	(0.8)	2	(1.4)	9	(0.8)
Other	0	(0.0)	3	(0.8)	8	(5.7)	11	(0.9)
Unknown	119	(18.1)	38	(10.4)	10	(7.1)	167	(14.3)

*Grouped by pneumococcal vaccine composition, less those included in vaccines of lower valency. 7v, 7-valent; 13v, 13-valent; 23v, 23-valent; PCV, pneumococcal conjugate vaccine; PPV, pneumococcal polysaccharide vaccine; VT, vaccine type.

Prior to universal infant vaccination, 7vPCV serotypes were the predominant (81%) cause of IPD (Table 4). After the substitution of 7vPCV with 13vPCV, 13vPCV (including 7vPCV) serotypes remained the major cause of IPD in children younger than 5 years of age (46%). The proportion of cases infected by additional serotypes contained in 23vPPV (19%) and non-vaccine-type serotypes (28%) since 2012 was considerably higher than during the targeted

7vPCV period (23vPPV, 2.4%; non-VT, 2.3%). Of the 64 PCV-type cases since 2012, 80% occurred in children aged 1–4 years.

Table 4—Infecting serotypes* (grouped by pneumococcal vaccine composition) of notified cases of invasive pneumococcal disease in children younger than 5 years by pneumococcal vaccine period and age group, Queensland, 2001–2015

	Targeted 7vPCV (2001–2004)		Universal 7vPCV (2005–2011)		Universal 13vPCV (2012–2015)		Total	
Age	n=658	(%)	n=367	(%)	n=140	(%)	n=1,165	(%)
<12 months	167	(25.4)	95	(25.9)	34	(24.3)	296	(25.4)
7vPCV	*129*	*(19.6)*	*23*	*(6.3)*	*6*	*(4.3)*	*158*	*(13.6)*
13vPCV	*20*	*(3.0)*	*44*	*(12.0)*	*7*	*(5.0)*	*71*	*(6.1)*
23vPPV	*9*	*(1.4)*	*13*	*(3.5)*	*9*	*(6.4)*	*31*	*(2.7)*
Non-VT	*6*	*(0.9)*	*9*	*(2.5)*	*9*	*(6.4)*	*24*	*(2.1)*
Unknown	*3*	*(0.5)*	*6*	*(1.6)*	*3*	*(2.1)*	*12*	*(1.0)*
12–23 months	284	(43.2)	128	(34.9)	45	(32.1)	457	(39.2)
7vPCV	*235*	*(35.7)*	*17*	*(4.6)*	*4*	*(2.9)*	*256*	*(22.0)*
13vPCV	*26*	*(4.0)*	*77*	*(21.0)*	*19*	*(13.6)*	*122*	*(10.5)*
23vPPV	*5*	*(0.8)*	*8*	*(2.2)*	*8*	*(5.7)*	*21*	*(1.8)*
Non-VT	*7*	*(1.1)*	*17*	*(4.6)*	*12*	*(8.6)*	*36*	*(3.1)*
Unknown	*11*	*(1.7)*	*9*	*(2.5)*	*2*	*(1.4)*	*22*	*(1.9)*
24–59 months	207	(31.5)	144	(39.2)	61	(43.6)	412	(35.4)
7vPCV	*172*	*(26.1)*	*31*	*(8.4)*	*5*	*(3.6)*	*208*	*(17.9)*
13vPCV	*21*	*(3.2)*	*72*	*(19.6)*	*23*	*(16.4)*	*116*	*(10.0)*
23vPPV	*2*	*(0.3)*	*11*	*(3.0)*	*10*	*(7.1)*	*23*	*(2.0)*
Non-VT	*2*	*(0.3)*	*22*	*(6.0)*	*18*	*(12.9)*	*42*	*(3.6)*
Unknown	*10*	*(1.5)*	*8*	*(2.2)*	*5*	*(3.6)*	*23*	*(2.0)*

*Grouped by pneumococcal vaccine composition, less those included in vaccines of lower valency. 7v, 7-valent; 13v, 13-valent; 23v, 23-valent; PCV, pneumococcal conjugate vaccine; PPV, pneumococcal polysaccharide vaccine; VT, vaccine type.

Over half of PCV-type cases since 2012 were caused by serotype 19A (Table 5). Additionally, half of all PCV-type cases in this period were cases of breakthrough IPD, all occurring in children aged 12–59 months. Since 2012, the burden of breakthrough IPD (32 cases) was more than double the burden of PCV-type disease in children younger than 12 months (13 cases).

Of the 13 infants younger than 12 months of age who experienced PCV-type disease since 2012, seven were younger than 2 months, four were aged 2–3 months, one was aged 4–5 months, and one was age 6 months. Three (23%) of

these cases had prematurity identified as a risk factor. Each of the six cases aged 2–5 months, and one case younger than 2 months, had received one 13vPCV dose. The single case aged 6 months had received two doses of 13vPCV, and their infection was caused by serotype 3.

Table 5—Characteristics of PCV-type* invasive pneumococcal disease in children younger than 5 years, Queensland, 2012–2015

Age	<12 months		12–23 months		24–59 months		Total	
	n=13	(%)	n=23	(%)	n=28	(%)	n=64	(%)
Sex								
Male	9	(69.2)	16	(69.6)	17	(60.7)	42	(65.6)
Female	4	(30.8)	7	(30.4)	11	(39.3)	22	(34.4)
Infecting serotype								
7vPCV	6	(46.2)	4	(17.4)	5	(17.9)	15	(23.4)
4	*0*	*(0.0)*	*1*	*(4.3)*	*0*	*(0.0)*	*1*	*(1.6)*
6B	*0*	*(0.0)*	*1*	*(4.3)*	*0*	*(0.0)*	*1*	*(1.6)*
18C	*1*	*(7.7)*	*0*	*(0.0)*	*1*	*(3.6)*	*2*	*(3.1)*
19F	*4*	*(30.8)*	*2*	*(8.7)*	*4*	*(14.3)*	*10*	*(15.6)*
9V	*1*	*(7.7)*	*0*	*(0.0)*	*0*	*(0.0)*	*1*	*(1.6)*
13vPCV	7	(53.8)	19	(82.6)	23	(82.1)	49	(76.6)
1	*0*	*(0.0)*	*0*	*(0.0)*	*2*	*(7.1)*	*2*	*(3.1)*
3	*3*	*(23.1)*	*2*	*(8.7)*	*3*	*(10.7)*	*8*	*(12.5)*
7F	*2*	*(15.4)*	*0*	*(0.0)*	*4*	*(14.3)*	*6*	*(9.4)*
19A	*2*	*(15.4)*	*17*	*(73.9)*	*14*	*(50.0)*	*33*	*(51.6)*
Breakthrough disease								
Yes	0	(0.0)	18	(78.3)	14	(50.0)	32	(50.0)
No death/unknown	13	(100.0)	5	(21.7)	14	(50.0)	32	(50.0)
Death due to IPD								
Yes	1	(7.7)	0	(0.0)	1	(3.6)	2	(3.1)
No	12	(92.3)	23	(100.0)	27	(96.4)	62	(96.9)
Clinical category								
Bacteraemia	7	(53.8)	9	(39.1)	7	(25.0)	23	(35.9)
Meningitis	2	(15.4)	0	(0.0)	1	(3.6)	3	(4.7)
Pneumonia	1	(7.7)	11	(47.8)	18	(64.3)	30	(46.9)
Other†	1	(7.7)	3	(13.0)	0	(0.0)	4	(6.3)
Unknown	2	(15.4)	0	(0.0)	2	(7.1)	4	(6.3)

*Cases of invasive pneumococcal disease caused by an infecting serotype contained in 13vPCV. †Includes septic arthritis (3) and mastoiditis (1). 7vPCV, 7-valent; 13v, 13-valent; IPD, invasive pneumococcal disease; PCV, pneumococcal conjugate vaccine

Breakthrough IPD

Forty-three cases of breakthrough IPD occurred from 2006 to 2015, the majority (74%) of which occurred since the replacement of 7vPCV with 13vPCV (Table 6). The greatest annual number of breakthrough cases occurred in 2015 (14) and 2013 (11) (Table 7). The median age of onset for breakthrough cases was 22.2 months (range, 10.5–57.7) and the time since last pneumococcal conjugate vaccine dose to onset of breakthrough disease ranged from 4.5 to 51.6 months (median, 14.3) (Figure 3).

Since 2012, over 60% of breakthrough cases were caused by serotype 19A, with serotype 19F (19%) the next most common cause of breakthrough disease. Bacterial pneumonia (51%) and bacteraemia (35%) were the most common clinical presentations reported in breakthrough cases, with only one (2%) case of breakthrough meningitis (3-year-old, serotype 3) identified.

Thirteen cases had received 3 doses of 7vPCV, 28 had 3 doses of 13vPCV, and one received 4 doses of 13vPCV. Two breakthrough cases (Case 5 and Case 28) in Indigenous children had received a dose of 23vPPV prior to illness onset. Case 5 had a congenital abnormality, prematurity, and household exposure to cigarette smoke identified as risk factors through enhanced surveillance. Household exposure to cigarette smoke was the only risk factor identified for Case 28. The single case who had received 4 doses of 13vPCV (Case 42) had a chromosomal disorder with associated immunosuppression and also attended childcare.

Overall, 56% of breakthrough cases had any risk factor identified through routine surveillance, significantly higher than in cases of non-breakthrough disease (Table 8). However, the proportion of notifications that attended childcare or had a congenital or chromosomal abnormality were the only individual risk factors that were significantly higher when comparing cases of breakthrough versus non-breakthrough disease. There was no significant difference in the proportion of Indigenous children with breakthrough (16.3%) and non-breakthrough (16.4%) disease ($\chi^2<0.001$; $p=0.98$).

Table 6—Characteristics of breakthrough invasive pneumococcal disease cases in children younger than 5 years by pneumococcal vaccine period, Queensland, 2005–2015

	Universal 7vPCV (2005–2011)		Universal 13vPCV (2012–2015)		Total	
	n=11	(%)	n=32	(%)	n=43	(%)
Age (months)						
<12	2	(18.2)	0	(0.0)	2	(4.7)
12–23	4	(36.4)	18	(56.3)	22	(51.2)
24–59	5	(45.5)	14	(43.8)	19	(44.2)
Sex						
Male	6	(54.5)	23	(71.9)	29	(67.4)
Female	5	(45.5)	9	(28.1)	14	(32.6)
Indigenous status						
Indigenous	2	(18.2)	5	(15.6)	7	(16.3)
Non-Indigenous	9	(81.8)	27	(84.4)	36	(83.7)
Death due to IPD						
Yes	0	(0.0)	1	(3.1)	1	(2.3)
No death/unknown	11	(100.0)	31	(96.9)	42	(97.7)
Infecting serotype						
7vPCV	11	(100.0)	7	(21.9)	18	(41.9)
4	*0*	*(0.0)*	*1*	*(3.1)*	*1*	*(2.3)*
6B	*2*	*(18.2)*	*0*	*(0.0)*	*2*	*(4.7)*
14	*1*	*(9.1)*	*0*	*(0.0)*	*1*	*(2.3)*
19F	*6*	*(54.5)*	*6*	*(18.8)*	*12*	*(27.9)*
23F	*2*	*(18.2)*	*0*	*(0.0)*	*2*	*(4.7)*
13vPCV	…	…	25	(78.1)	25	(58.1)
3	…	…	*5*	*(15.6)*	*5*	*(11.6)*
19A	…	…	*20*	*(62.5)*	*20*	*(46.5)*
Clinical category						
Bacteraemia	6	(54.5)	9	(28.1)	15	(34.9)
Meningitis	0	(0.0)	1	(3.1)	1	(2.3)
Pneumonia	4	(36.4)	18	(56.3)	22	(51.2)
Other*	0	(0.0)	3	(9.4)	3	(7.0)
Unknown	1	(9.1)	1	(3.1)	2	(4.7)

*Includes septic arthritis (2) and mastoiditis (1). 7v, 7-valent; 13v, 13-valent; IPD, invasive pneumococcal disease; PCV, pneumococcal conjugate vaccine.

Table 7—Line list of breakthrough invasive pneumococcal disease cases in children younger than 5 years of age, Queensland, 2006–2015

Case	Year	Age (months)	Indigenous status	Infecting serotype	7vPCV doses	13vPCV doses	Months since last PCV dose
1	2006	17	Non-Indigenous	19F	3	0	10
2	2006	18	Non-Indigenous	19F	3	0	12
3	2006	11	Non-Indigenous	23F	3	0	5
4	2007	14	Non-Indigenous	6B	3	0	6
5*	2008	27	Indigenous	23F	3	0	19
6	2008	25	Non-Indigenous	6B	3	0	18
7	2008	16	Indigenous	19F	3	0	10
8	2009	57	Non-Indigenous	14	3	0	51
9	2010	56	Non-Indigenous	19F	3	0	50
10	2011	33	Non-Indigenous	19F	3	0	29
11	2011	10	Non-Indigenous	19F	3	0	4
12	2012	46	Non-Indigenous	19F	3	0	40
13	2012	23	Non-Indigenous	4	3	0	16
14	2013	16	Non-Indigenous	19A	0	3	10
15	2013	18	Non-Indigenous	3	0	3	12
16	2013	18	Non-Indigenous	19A	0	3	12
17	2013	15	Non-Indigenous	19A	0	3	8
18	2013	17	Indigenous	19A	0	3	11
19	2013	23	Non-Indigenous	19A	0	3	16
20	2013	22	Non-Indigenous	19A	0	3	16
21	2013	19	Non-Indigenous	19F	0	3	10
22	2013	21	Non-Indigenous	19A	0	3	14
23	2013	13	Indigenous	19A	0	3	6
24	2013	27	Non-Indigenous	3	0	3	21
25	2014	24	Non-Indigenous	19A	0	3	18
26	2014	15	Non-Indigenous	19A	0	3	9
27	2014	27	Non-Indigenous	3	0	3	20
28*	2014	25	Indigenous	3	0	3	18
29	2014	38	Non-Indigenous	19F	0	3	32
30	2015	35	Non-Indigenous	19A	0	3	28
31	2015	40	Non-Indigenous	19A	0	3	33
32	2015	17	Indigenous	3	0	3	10
33	2015	39	Non-Indigenous	19A	0	3	33
34	2015	18	Non-Indigenous	19A	0	3	12
35	2015	33	Non-Indigenous	19A	0	3	27
36	2015	51	Non-Indigenous	19F	2	1	45
37	2015	15	Non-Indigenous	19A	0	3	9
38	2015	14	Non-Indigenous	19A	0	3	9
39	2015	13	Non-Indigenous	19F	0	3	7
40	2015	20	Indigenous	19A	0	3	12
41	2015	28	Non-Indigenous	19A	0	3	12
42	2015	37	Non-Indigenous	19F	0	4	17
43	2015	35	Non-Indigenous	19A	0	3	29

*Also received 1 dose of 23-valent pneumococcal polysaccharide vaccine. 7v, 7-valent; 13v, 13-valent; PCV, pneumococcal conjugate vaccine.

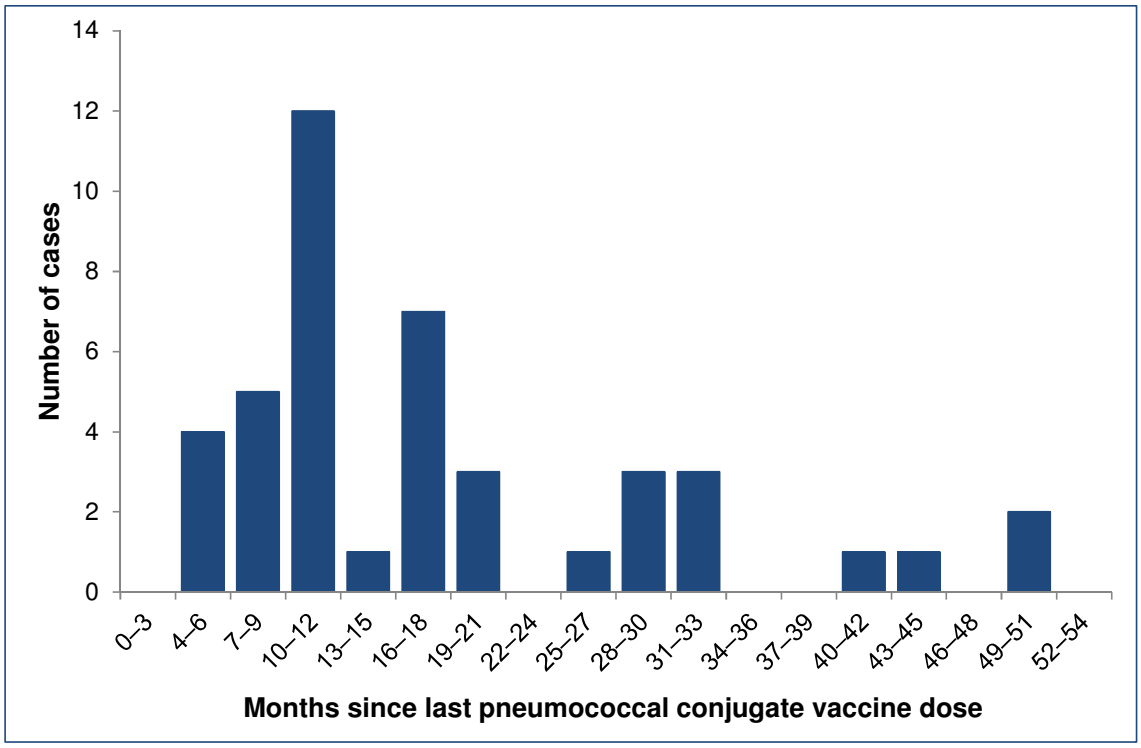


Figure 3—Months elapsed since last pneumococcal conjugate vaccine dose among cases of breakthrough invasive pneumococcal disease in children younger than 5 years of age, Queensland, 2006–2015

Table 8—Risk factors identified through routine surveillance for breakthrough and non-breakthrough cases of invasive pneumococcal disease in children younger than 5 years, Queensland, 2006–2015

	Breakthrough cases		Non-breakthrough cases			
Risk factor	n=43	(%)	n=408	(%)	χ^2	p-value*
Any risk factor identified	24	(55.8)	117	(28.7)	13.3	<0.001
Childcare attendee	17	(39.5)	20	(4.9)	62.0	<0.001
Household exposure to cigarette smoke	4	(9.3)	42	(10.3)	2.2	0.16
Prematurity (<37 weeks gestation)	4	(9.3)	39	(9.6)	0.0	1.00
Presence of a congenital or chromosomal abnormality	4	(9.3)	11	(2.7)	5.3	0.04
Immunocompromised	3	(7.0)	18	(4.4)	0.6	0.44
Presence of a chronic illness	1	(2.3)	11	(2.7)	0.0	1.00

*Calculated using Fisher's exact test.

Recurrent IPD

From 1997 to 2015, there were 6,075 notified cases of IPD reported in 5,955 Queensland residents. Of these, 120 (2%) were recurrent episodes that occurred in 102 individuals (Table 9). Among those who had disease recurrence, 87 (85%) experienced two episodes, 13 (13%) had three episodes, one (1%) person experienced four episodes, and one (1%) had five episodes recorded. A total of 5,490 (92%) individuals survived more than 14 days after their initial IPD episode, contributing 45,394 person-years at risk of recurrent disease.

The annual rate of primary IPD during the study period was 7.8 per 100,000, and was lowest from 2012–2015 (5.6 per 100,000). The overall rate of recurrent IPD was 264.4 per 100,000 person-years, 35 times the annual incidence of primary IPD. The recurrence rate was highest from 2001–2004, decreasing by 50% from 2005–2011, and subsequently increasing 36% during the 2012–2015 period, when the recurrence rate was 50 times the annual incidence of primary IPD. The median time elapsed between the first and second episode was 19.8 months (range, 27 days–12.3 years; Figure 4). Thirty-five (34%) individuals had their second episode within 12 months of their initial episode. For further recurrence (>2 episodes), the median period between episodes was 25.5 months (range, 55 days–4.3 years). The rate of any recurrence after a second episode of IPD was 3,592.7 per 100,000 person-years (95% CI, 2,263.5–5,702.3). At the time of the second episode, 70% of individuals had no record of pneumococcal vaccination.

The recurrent IPD rate among Indigenous Australians (991.1 per 100,000 person-years) was approximately four times the rate in the non-Indigenous population, and over 100 times the primary IPD rate. While not significant, the IPD recurrence rate following an initial episode of pneumococcal meningitis was nearly double that after a primary episode of pneumococcal bacteraemia or bacteraemic pneumonia. The clinical categories of recurrent episodes were significantly different according to the category of the initial episode (χ^2, 64.6; $p<0.001$;

Table 10), with individuals most likely to experience a recurrent episode of the same category as their initial presentation.

Table 9—Characteristics and rates of recurrent and primary invasive pneumococcal disease cases, Queensland, 1997–2015

	Recurrent disease			Primary disease	
	n=120 (%)	Rate*	(95% CI)	n=5,955 (%)	Rate†
Age (years)					
<5	8 (6.7)	166.1	(83.1–332.1)	1,596 (26.8)	30.6
5–14	12 (10.0)	89.6	(50.9–157.8)	327 (5.5)	3.1
15–49	51 (42.5)	376.9	(286.4–495.9)	1,553 (26.1)	4.1
50–64	27 (22.5)	465.8	(319.5–679.3)	1,016 (17.1)	7.7
≥65	22 (18.3)	280.5	(184.7–426.0)	1,462 (24.6)	15.3
Sex					
Male	64 (53.3)	253.4	(198.3–323.7)	3,294 (55.3)	8.6
Female	56 (46.7)	278.4	(214.2–361.7)	2,660 (44.7)	6.9
Indigenous status					
Indigenous	54 (45.0)	979.9	(750.5–1,279.4)	756 (12.7)	27.5
Non-Indigenous	66 (55.0)	165.5	(130.0–210.6)	5,199 (87.3)	6.9
Clinical category‡					
Bacteraemia	25 (20.8)	339.98	(229.7–503.2)	989 (16.6)	1.3
Meningitis	9 (7.5)	670.14	(348.7–1,288.0)	222 (3.7)	0.3
Pneumonia	33 (27.5)	359.8	(255.8–506.1)	1,769 (29.7)	2.3
Other/unknown	53 (44.2)	192.5	(147.1–252.0)	2,975 (50.0)	3.9
Time period					
1997–2000	4 (3.3)	268.8	(100.9–716.2)	1,103 (18.5)	8.0
2001–2004	27 (22.5)	409.4	(280.8–597.0)	1,772 (29.8)	12.0
2005–2011	44 (36.7)	206.6	(153.8–277.7)	2,033 (34.1)	6.9
2012–2015	45 (37.5)	280.4	(209.3–375.5)	1,047 (17.6)	5.6
1997–2015	120 (100.0)	264.4	(221.0–316.1)	5,955 (100.0)	7.8

*Per 100,000 person-years. †Per 100,000 population per year. ‡For recurrent disease, the clinical category represents that of the initial episode, with the number of cases and recurrence rates following an initial episode of the specified clinical presentation of IPD.

Table 10—Clinical category of initial and recurrent episodes of invasive pneumococcal disease, Queensland, 1997–2015

Category of initial episode	Category of recurrent episodes				
	Bacteraemia	Meningitis	Pneumonia	Other/unknown	Total
	n (%)	n (%)	n (%)	n (%)	n (%)
Bacteraemia	14 (56.0)	0 (0.0)	5 (20.0)	6 (24.0)	25 (100.0)
Meningitis	1 (11.1)	4 (44.4)	1 (11.1)	3 (33.3)	9 (100.0)
Pneumonia	11 (33.3)	0 (0.0)	17 (51.5)	5 (15.2)	33 (100.0)
Other/unknown	7 (13.2)	2 (3.8)	12 (22.6)	32 (60.4)	53 (100.0)

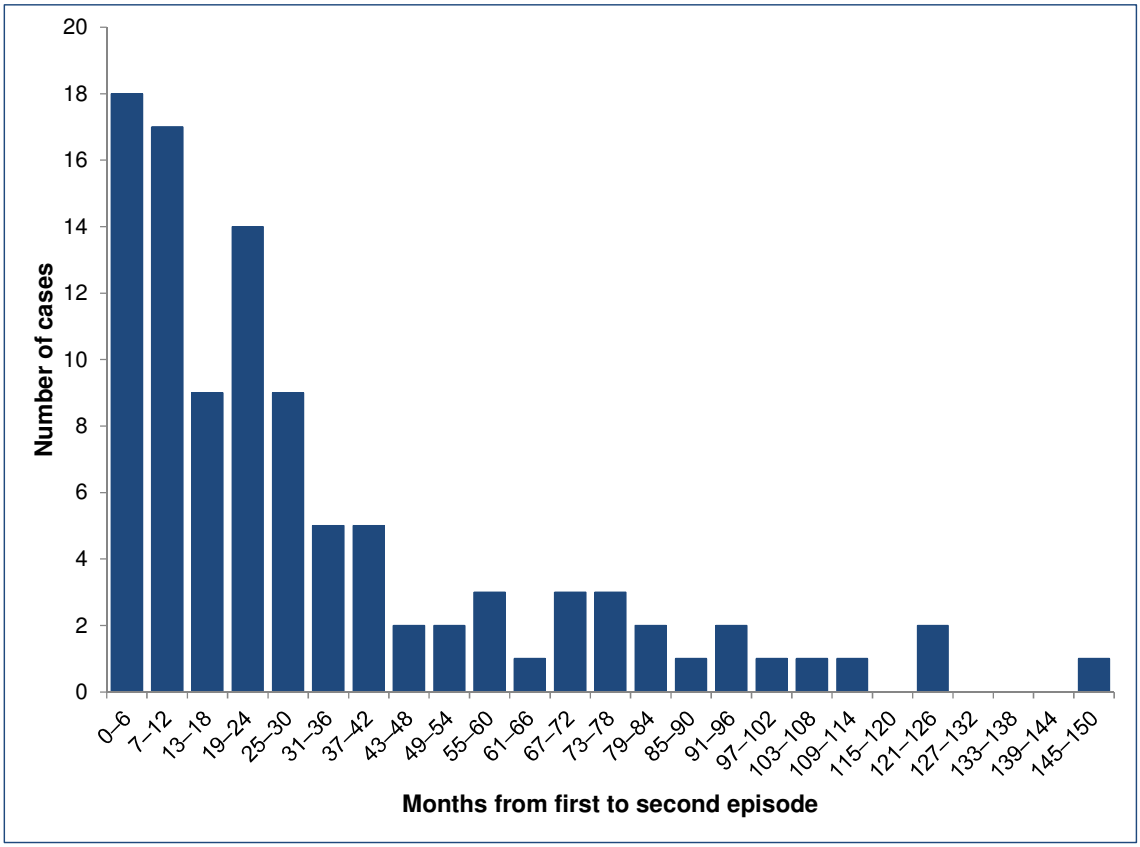


Figure 4—Months elapsed between onset of first and second episodes of invasive pneumococcal disease, Queensland, 1997–2015

Forty-eight percent of individuals with recurrent IPD had no risk factor identified at the time of their initial episode (Table 11). This group experienced a recurrence rate of 168.0 per 100,000 person-years (95% CI, 129.6–217.9). Those with any risk factor identified at the time of the first episode had a recurrence rate of 549.1 per 100,000 person-years (95% CI, 428.9–702.8)

Table 11—Risk factors identified for individuals with recurrent and primary-only invasive pneumococcal disease, Queensland, 1997–2015

	Recurrent disease†		Primary-only disease	
Risk factor*	n=102	(%)	n=5,853	(%)
No risk factor identified	49	(48.0)	3,391	(57.9)
Chronic disease	30	(29.4)	956	(16.3)
Current smoker	21	(20.6)	478	(8.2)
Excessive alcohol consumption‡	14	(13.7)	304	(5.2)
Aged ≥65 years, non-Indigenous	13	(12.7)	1,402	(24.0)
Immunosuppression	10	(9.8)	324	(5.5)
Diabetes	8	(7.8)	181	(3.1)
Aged ≥50 years, Indigenous	6	(5.9)	147	(2.5)
Prematurity (<37 weeks gestation)	3	(2.9)	109	(1.9)
Functional or anatomical asplenia	2	(2.0)	53	(0.9)

*Individuals may have more than one risk factor identified. †Risk factors for individuals with recurrent disease identified at the time of the first episode. ‡Defined as ≥4 standard drinks/day for females and ≥6 standard drinks/ day for males.

From 2012 onwards, one-third of recurrent episodes were caused by 13vPCV serotypes, and an additional 27% were caused by the additional serotypes contained in 23vPPV (Table 12).

Table 12—Infecting serotypes of recurrent invasive pneumococcal disease cases by pneumococcal vaccine period, Queensland, 1997–2015

Infecting serotype*	**Pre-7vPCV** (1997–2000)		**Targeted 7vPCV** (2001–04)		**Universal 7vPCV** (2005–11)		**Universal 13vPCV** (2012–15)		**Total**	
	n=4	(%)	n=27	(%)	n=44	(%)	n=45	(%)	n=120	(%)
7vPCV	0	(0.0)	17	(63.0)	13	(29.5)	5	(11.1)	35	(29.2)
13vPCV	0	(0.0)	3	(11.1)	11	(25.0)	10	(22.2)	24	(20.0)
23vPPV	0	(0.0)	3	(11.1)	7	(15.9)	12	(26.7)	22	(18.3)
Non-VT	0	(0.0)	3	(11.1)	11	(25.0)	18	(40.0)	32	(26.7)
Unknown	4	(100.0)	1	(3.7)	2	(4.5)	0	(0.0)	7	(5.8)

*Grouped by pneumococcal vaccine composition, less those included in vaccines of lower valency. 7v, 7-valent; 13v, 13-valent; 23v, 23-valent; PCV, pneumococcal conjugate vaccine; PPV, pneumococcal polysaccharide vaccine; VT, vaccine type.

Cox proportional hazards analyses

Age younger than 15 years

In cases younger than 15 years, the risk factors associated with the highest risk of recurrence were immunocompromising conditions (HR, 12.64; 95% CI, 4.18–38.22) and presence of a chronic illness (HR, 9.99; 95% CI, 2.91–34.33; Table 13).

After adjustment, risk factors identified at the time of the first episode associated with a significantly increased risk of recurrent disease included age group, Indigenous status, presence of immunocompromising conditions, presence of a chronic illness, and prematurity (Table 14).

For each covariate included in the final multivariate model, ln-ln survival plots and plots of Kaplan-Meier observed survival curves against Cox predicted curves demonstrated parallel, non-intersecting curves across strata. The final multivariate model also did not violate the assumption of a constant log hazard ratio function (p=0.42).

Table 13—Crude HRs for recurrent invasive pneumococcal disease by covariates at the time of the first episode in those younger than 15, Queensland, 1997–2015

	Primary cases	Recurrent cases	HR (95% CI)	p-value (Wald)	p-value (LRT)
Sex					
Female	783	7	1.00	···	0.67
Male	1,099	12	1.22 (0.48–3.10)	0.67	···
Age (years)					
<5	1,559	11	1.00	···	0.13
5–14	324	8	3.62 (1.46–9.01)	0.006	···
Indigenous status					
Non-Indigenous	1,615	11	1.00	···	0.003
Indigenous	268	8	4.52 (1.82–11.25)	0.001	···
Time period					
1997–2000	503	3	1.00	···	0.64
2001–2004	726	8	1.85 (0.49–6.97)	0.36	···
2005–2011	457	6	2.28 (0.57–9.12)	0.25	···
2012–2015	197	2	2.31 (0.38–13.97)	0.36	···
Clinical category					
Bacteraemia	606	5	1.00	···	0.69
Meningitis	103	2	2.47 (0.48–12.71)	0.28	···
Pneumonia	412	3	0.91 (0.22–3.81)	0.90	···
Other/unknown	762	9	1.40 (0.47–4.19)	0.54	···
Infecting serotype*					
7vPCV	698	6	1.00	···	0.064
13vPCV	405	4	1.22 (0.34–4.32)	0.76	···
23vPPV	85	1	1.54 (0.18–12.78)	0.69	···
Non-VT	129	5	5.17 (1.57–16.98)	0.007	···
Unknown	566	3	0.61 (0.15–2.45)	0.49	···
Previous pneumococcal vaccination					
None	1,402	13	1.00	···	0.41
Present	481	6	1.52 (0.57–4.00)	0.40	···
Household exposure to cigarette smoke					
None	1,745	17	1.00	···	0.582
Present	138	2	1.55 (0.36–6.69)	0.56	···
Immunocompromising condition					
None	1,833	15	1.00	···	<0.001
Present	50	4	12.64 (4.18–38.22)	<0.001	···
Chronic illness					
None	1,841	16	1.00	···	0.005
Present	42	3	9.99 (2.91–34.33)	<0.001	···
Prematurity (<37 weeks gestation)					
None	1,778	16	1.00	···	0.10
Present	105	3	3.27 (0.95–11.23)	0.060	···

*Of the first disease episode, grouped by pneumococcal vaccine composition, less those included in vaccines of lower valency. 7v, 7-valent; 13v, 13-valent; 23v, 23-valent; HR, hazard ratio; LRT, likelihood ratio test, PCV, pneumococcal conjugate vaccine; PPV, pneumococcal polysaccharide vaccine; VT, vaccine type.

Table 14—Adjusted HRs for recurrent invasive pneumococcal disease by covariates at the time of the first episode in those younger than 15 years, Queensland, 1997–2015

	Primary cases	Recurrent cases	Adjusted HR* (95% CI)	p-value (Wald)	p-value (LRT)
Age (years)					
<5	1,559	11	1.00	···	0.052
5–14	324	8	2.69 (1.03–7.04)	0.044	···
Indigenous status					
Non-Indigenous	1,615	11	1.00	···	0.012
Indigenous	268	8	3.58 (1.39–9.23)	0.008	···
Immunocompromising condition					
None	1,833	15	1.00	···	0.005
Present	50	4	8.40 (2.37–29.81)	0.001	···
Chronic illness					
None	1,841	16	1.00	···	0.069
Present	42	3	4.21 (1.06–16.75)	0.041	···
Prematurity (<37 weeks gestation)					
None	1,778	16	1.00	···	0.10
Present	105	3	3.28 (0.93–11.59)	0.065	···

*Adjusted for variables shown in the table. HR, hazard ratio; LRT, likelihood ratio test.

Aged 15 years or more

For cases aged 15 years or more at the time of the first episode of IPD, factors associated with the highest risk of recurrence were previous pneumococcal vaccination (HR, 5.37; 95% CI, 3.21–8.97), being an Indigenous Australian (HR, 5.04; 95% CI, 3.24–7.82), and household exposure to cigarette smoke (HR, 4.92; 95% CI, 2.14–11.30; Table 15). Each of the 19 individuals with recurrent disease and previous vaccination were Indigenous Australians.

Adjusted variables significantly associated with recurrent disease were being an Indigenous Australian, category of clinical primary IPD episode, household exposure to cigarette smoke, and presence of a chronic illness. Inclusion of both age and sex were neither significant nor resulted in a substantial (≥10%) change to the coefficients in the final multivariate model and were excluded (Table 16).

For each covariate included in the final multivariate model, ln-ln survival plots and plots of Kaplan-Meier observed survival curves against Cox predicted curves demonstrated parallel, non-intersecting curves across strata. The final multivariate model also did not violate the assumption of a constant log hazard ratio function (p=0.74).

Table 15—Crude HRs for recurrent invasive pneumococcal disease by covariates at the time of the first episode in those aged 15 years or more, Queensland, 1997–2015

	Primary cases	Recurrent cases	HR (95% CI)	p-value (Wald)	p-value (LRT)
Sex					
Female	1,676	40	1.00	···	0.79
Male	1,930	43	0.94 (0.61–1.45)	0.79	···
Age (years)					
15–49	1,473	43	1.00	···	0.13
50–64	931	25	1.13 (0.69–1.86)	0.62	···
≥65	1,202	15	0.62 (0.34–1.11)	0.11	···
Indigenous status					
Non-Indigenous	3,164	50	1.00	···	<0.001
Indigenous	442	33	5.04 (3.24–7.82)	<0.001	···
Time period					
1997–2000	513	12	1.00	···	0.11
2001–2004	936	25	1.18 (0.59–2.35)	0.64	···
2005–2011	1,395	30	1.17 (0.59–2.30)	0.66	···
2012–2015	762	16	2.43 (1.11–5.32)	0.026	···
Clinical category					
Bacteraemia	325	16	1.00	···	<0.001
Meningitis	128	4	0.54 (0.18–1.62)	0.27	···
Pneumonia	1,233	25	0.35 (0.19–0.66)	0.001	···
Other/unknown	1,920	38	0.25 (0.14–0.45)	<0.001	···
Infecting serotype*					
7vPCV	1,040	21	1.00	···	0.010
13vPCV	902	18	1.31 (0.69–2.47)	0.41	···
23vPPV	494	14	2.03 (1.03–4.02)	0.04	···
Non-VT	493	17	2.86 (1.49–5.46)	0.001	···
Unknown	677	13	0.93 (0.46–1.85)	0.83	···
Previous pneumococcal vaccination					
None	3,370	64	1.00	···	<0.001
Present	236	19	5.37 (3.21–8.97)	<0.001	···
Smoking status					
Never smoked	2,859	59	1.00	···	0.002
Ex-smoker	298	3	0.65 (0.20–2.07)	0.46	···
Current smoker	449	21	2.54 (1.54–4.18)	<0.001	···
Household exposure to cigarette smoke					
None	3,556	77	1.00	···	0.002
Present	50	6	4.92 (2.14–11.30)	<0.001	···
Functional or anatomical asplenia					
None	3,561	81	1.00	···	0.23
Present	45	2	2.71 (0.67–11.02)	0.16	···
Excessive alcohol consumption					
None	3,328	69	1.00	···	0.001
Present	278	14	2.88 (1.62–5.12)	<0.001	···
Immunocompromising condition					
None	3,356	77	1.00	···	0.26
Present	250	6	1.67 (0.72–3.84)	0.23	···
Chronic illness					
None	2,790	56	1.00	···	<0.001
Present	816	27	2.56 (1.61–4.08)	<0.001	···

*Grouped by pneumococcal vaccine composition, less those included in vaccines of lower valency. 7v, 7-valent; 13v, 13-valent; 23v, 23-valent; HR, hazard ratio; LRT, likelihood ratio test; PCV, pneumococcal conjugate vaccine; PPV, pneumococcal polysaccharide vaccine; VT, vaccine-type.

Table 16—Adjusted HRs for recurrent invasive pneumococcal disease by covariates at the time of the first episode in those aged 15 years or more, Queensland, 1997–2015

	Primary cases	Recurrent cases	Adjusted HR* (95% CI)	p-value (Wald)	p-value (LRT)
Indigenous status					
Non-Indigenous	3,164	50	1.00	···	<0.001
Indigenous	442	33	4.32 (2.71–6.87)	<0.001	···
Clinical category					
Bacteraemia	325	16	1.00	···	0.015
Meningitis	128	4	0.67 (0.22–2.02)	0.48	···
Pneumonia	1,233	25	0.34 (0.18–0.64)	0.001	···
Other/unknown	1,920	38	0.53 (0.26–1.04)	0.067	···
Household exposure to cigarette smoke					
None	3,556	77	1.00	···	0.025
Present	50	6	3.12 (1.31–7.40)	0.010	···
Chronic illness					
None	2,790	56	1.00	···	0.008
Present	816	27	2.14 (1.22–3.77)	0.008	···

*Adjusted for variables shown in the table.
HR, hazard ratio; LRT, likelihood ratio test

Discussion

Breakthrough IPD

The burden of IPD in Queensland children younger than 5 years of age has significantly decreased following the introduction of universal infant vaccination with PCVs, in-line with national trends.[39] However, since the replacement of 7vPCV with 13vPCV in the NIP, breakthrough disease has emerged as the major cause of preventable IPD in this age group. Additionally, the burden of breakthrough disease in children aged 1–4 years has surpassed the total burden of PCV-type disease in children younger than 12 months. Similar increases in breakthrough disease have not been observed in other countries after replacement of 7vPCV with 13vPCV that use 2+1 or 3+1 schedules in their national immunisation programs.[40-42] The factors most likely contributing to the increase in breakthrough IPD that we observed, including the vaccine, the schedule, and underlying conditions, require further examination.

Breakthrough IPD has further increased since the introduction of 13vPCV, with the most likely explanation for this being reduced vaccine effectiveness against certain serotypes using a 3+0 schedule. The increase in breakthrough IPD has been primarily driven by serotypes 19A and 3, though serotype 19F also has been responsible for breakthrough disease after primary courses of both 7vPCV and 13vPCV. Vaccine effectiveness of 13vPCV in children against serotype 3 has been shown in general to be nonsignificant, and against serotype 19A is considerably lower than other 7vPCV and 13vPCV serotypes.[43-46] The reduced serotype-specific effectiveness likely contributes in part to the persistence of 19A and 3 as the predominant infecting serotypes observed both in our study and overseas since the introduction of 13vPCV.[47] In contrast, immunogenicity and reduction in nasopharyngeal colonisation specific to serotype 19F have been demonstrated to be superior after a primary course and booster dose of 13vPCV compared to 7vPCV.[48,49] Absence of a booster dose at or after 12-months of age in the NIP may therefore partly explain the continued occurrence of

breakthrough 19F cases, despite the demonstrated effectiveness of 13vPCV against this serotype.

The effect of vaccine scheduling on immunogenicity and carriage also influences the likelihood of breakthrough disease. Most studies examining the effects of pneumococcal vaccine scheduling on these outcomes were performed in settings where 7vPCV was being used. Three primary 7vPCV doses have been shown to produce higher proportions of children with protective antibody levels than in children receiving 2 primary doses by seven months of age, though these differences largely disappear by 12 months.[17] Post-boosting antibody concentrations at 13 months and 19 months are significantly higher in those receiving a 2+1 compared to a 3+0 schedule.[50] Significant differences have not been seen in rates of carriage between 3+0 and 2+1 schedules, though these have not been evaluated for 13vPCV serotypes beyond the first year of life when the incidence of breakthrough disease increases.[19] While these comparisons are not necessarily generalisable to the serotype-specific immune responses induced by 13vPCV, they are indicative of lower long-term protection provided by a 3+0 schedule. Previous evidence of lower vaccine effectiveness against serotypes 19A and 3, combined with waning immunity beyond the first year of life coheres with our experience of children with breakthrough disease at a median age of 22 months, 14 months since their most recent PCV dose. The evidence for greater long-term antibody concentrations resulting from booster dose schedules and the timing of breakthrough disease in our study suggests that a 2+1 schedule may be of benefit in reducing the burden of breakthrough IPD in our population.

Underlying immunocompromising conditions may also lead to reduced pneumococcal vaccine effectiveness and subsequent breakthrough disease.[51] In our study, childcare attendance was the predominant risk factor we identified in children with breakthrough disease. While the proportion of breakthrough cases with a congenital or chromosomal abnormality was higher compared to non-breakthrough cases, less than 10 per cent of breakthrough cases had these risk factors identified. One reason for this might be that children with underlying medical conditions are already provided a booster 13vPCV dose at 12 months,

conferring sufficient long-term immunity to prevent breakthrough disease during the high-risk period from 12 to 23 months of age. If underlying medical conditions were a significant contributor to the burden of breakthrough IPD, we would have expected a higher frequency of cases in the Australian 7vPCV era, as well as greater numbers of breakthrough disease reported from overseas countries.[40]

An essential consideration in changing from a 3+0 to 2+1 schedule is that, by removing the third primary dose, the risk of PCV-type disease may, theoretically, increase in children from 6 months of age until receipt of the 12-month booster dose. Serotype-specific antibody concentrations are typically higher after receiving 3 compared to 2 primary doses in the first year of life.[17] However, the proportion of children achieving protective antibody concentrations during this period are similar in both schedules.[17,52] We found the burden of PCV-type disease in children aged 6–12 months to be small, with only one child experiencing an episode of IPD due to serotype 3 in this age group since 2012. With the herd protection achieved through high vaccination coverage and low case numbers in those aged 6–12 months, the risk of increased disease caused by changing to a 2+1 schedule is likely low.

Cases of breakthrough disease in Australia (identified as pneumococcal vaccine failures) are reported in quarterly and annual IPD surveillance reports by the Enhanced Invasive Pneumococcal Disease Surveillance Working Group (EIPDSWG). However, no surveillance reports have summarised trends in pneumococcal vaccine failures following the introduction of 7vPCV and subsequent replacement with 13vPCV. In 2016, a total of 43 13vPCV failures were reported nationally in children younger than 5 years, accounting for 70% of the IPD burden in this age group.[53-56] This is considerably higher than the proportion of the IPD burden due to breakthrough disease we observed from 2012–2015 (50%), though this may be due to the difference in definitions of breakthrough disease used in our study and the definition of vaccine failure

used by EIPDSWG.[†] Of the 43 nationally reported cases of 13vPCV failures in 2016, 15 (35%) were caused by each of serotypes 19A and 3, and 11 (26%) were caused by serotype 19F. This serotype distribution of breakthrough disease is similar to that in our study from 2012–2015, except for the notably higher proportion of national cases caused by serotype 3 (35% vs. 12%). The high proportion of national PCV-type disease due to vaccine failures is concerning and highlights this issue is persisting and not isolated to the Queensland population.

Recurrent IPD

We identified recurrent episodes in 2% of those experiencing a primary episode of IPD, similar to that reported in previous studies of recurrent invasive disease.[1,23,25,26] However, individuals with a previous episode of IPD experience a substantially increased risk of future disease compared to the general population. Recurrence rates were higher among certain groups such as Indigenous Australians and those with underlying medical conditions, but also remain elevated in individuals with no underlying risk factors identified through enhanced surveillance. The elevated risk of recurrence in those without known risk factors is concerning, as this group is currently neglected in pneumococcal vaccination recommendations. Given the severity of the disease, high rates of recurrence, and potential for preventability, the association between previous IPD and future disease should be recognised and reflected in national immunisation guidelines.

Considerations regarding the number, timing, and pneumococcal vaccine type to provide individuals after an episode of IPD primarily include age and

[†] Vaccine failures used by the EIPDSWG and reported nationally include children aged more than 6 months of age that received 3 or more doses of a PCV and develop IPD due to a serotype contained within all 3 doses of the administered conjugate vaccines. Also included are those aged 6 months or more who receive less than 3 doses of a PCV due to a delayed start, missed doses, or catch-up, but the total number of doses is age-appropriate according to the recommendations in the *Australian Immunisation Handbook*.

previous pneumococcal vaccination history. The presence of underlying medical conditions may also influence the decision regarding type and number of doses, as immune responses might be suboptimal in certain groups or populations. Protective immune responses have been demonstrated in patients receiving 13vPCV after an episode of *S. pneumoniae* CAP, suggesting that individuals with previous pneumococcal disease might also produce protective antibody levels to vaccine-specific serotypes.[57] Recommendations from Spleen Australia for vaccination of children and adults with asplenia or hyposplenism[58,59] (Box 1) could be applied to those with previous IPD and may guide the development of guidelines for vaccination in this group. Catch-up schedules for 13vPCV also exist for children younger than 2 years with medical conditions at increased risk of IPD[60] that could be applied to those with an initial IPD episode in this age group.

Box 1—Spleen Australia pneumococcal vaccine recommendations for people with asplenia or hyposplenism[58,59]

Age <5 years	
13vPCV	Primary course at 2, 4, 6 months of age as per NIP
	Booster dose at 12 months of age
23vPPV	1 dose at 4–5 years of age
Age 5–18 years	
13vPCV	1 dose if no previous doses since 12 months of age
23vPPV	1 dose >8 weeks post 13vPCV dose (if no previous 23vPPV)
	Booster dose 5 years post 1st 23vPPV dose
Age >18 years with no previous pneumococcal vaccination	
13vPCV	1 dose
23vPPV	1 dose 8 weeks post 13vPCV
	Booster dose 5 years post 23vPPV
Age >18 years with previous 13vPCV	
13vPCV	1 dose*
23vPPV	1 dose 8 weeks post 13vPCV
	Booster dose 5 years post 23vPPV
Age >18 years with previous 23vPPV	
13vPCV	1 dose >1 year post previous 23vPPV dose
23vPPV	1 dose 5 years post previous 23vPPV dose

*At least 8 weeks must have passed since any previous 13vPCV dose. 13v, 13-valent; 23, 23-valent; PCV, conjugate vaccine; PPV, pneumococcal polysaccharide vaccine; NIP, National Immunisation

With over one-third of those with disease recurrence experiencing their second episode within 12 months of their initial episode of IPD, pneumococcal vaccination should be commenced as soon as practical after recovery from the

initial episode. This of particular importance in children, as a primary episode of IPD can signify underlying immunodeficiency.[61] The majority (70%) of individuals had no record of any pneumococcal vaccination at the time of their second episode, despite over half with identifiable risk factors at the time of the initial episode, highlighting the need for increased coverage in this group. Recurrence rates were highest in the period prior to the introduction of universal infant vaccination with 7vPCV. The subsequent decline in the recurrence rates is likely to have occurred as a result of both direct and indirect protection among those with previous IPD. However, the reduction in recurrence rates was not proportionate to the declines observed in the rate of primary disease during the same period. The observed disproportionate decline in recurrence rates is likely multifactorial, and may reflect underlying factors placing individuals at ongoing increased risk of disease, poor vaccination coverage in those at risk of recurrence, or differences in environmental factors that increase risk of disease. Planning of pneumococcal vaccination by treating medical practitioners during any primary or recurrent IPD episode, while cases are engaged with the health system and potentially motivated by their illness, would likely improve uptake and timeliness of pneumococcal vaccination. The risk of recurrence and any changes to pneumococcal vaccination recommendations should be communicated with healthcare providers to support successful implementation of this strategy.

Nearly half of all recurrent episodes occurred in Indigenous Australians, who experienced the highest crude rates of recurrent disease and were at significantly increased risk of disease after adjustment for other factors. While 3-dose coverage at 12 months of age with 13vPCV in Indigenous children has been relatively high (86% Australia-wide in 2014), uptake of the recommended 12-to-18-month 13vPCV booster dose appears to have been considerably lower (67% Australia-wide in 2014, assessed at 30 months of age).[10] Vaccination coverage with 23vPPV in Indigenous adults is not routinely reported, though previous estimates of coverage in the Northern Territory demonstrated relatively low uptake with considerable regional variation (24–64%).[62] Increased uptake of the childhood booster dose and adult 23vPPV dose would likely lead to a decrease in both primary and recurrent IPD in the Indigenous

population. A targeted catch-up program for Indigenous children and adults with previous IPD would likely assist in reducing the disproportionately high risk of recurrence experienced in the Indigenous population.

An initial episode of pneumococcal meningitis was associated with a lower (though not statistically significant) risk of recurrence in those aged 15 years or more when compared to an initial episode of bacteraemia. The opposite effect was observed in children and adolescents younger than 15 years of age, though this was also not statistically significant. However, an initial episode of invasive pneumococcal pneumonia was associated with a decreased risk (-65%) of recurrence compared with bacteraemia, in individuals aged 15 years or more, which remained significant after adjustment. The significance of this finding is unclear, and may be due to misclassification of clinical categories or residual confounding in our model. Despite the lower associated recurrence risk after an initial episode of IPD pneumonia, the crude rate in this group was still substantially elevated (360 per 100,000 person-years). Given this, our findings do not suggest that the clinical presentation of the initial IPD episode should influence the decision of who should receive pneumococcal vaccines. Future studies of IPD recurrence might elucidate this relationship further if sufficiently powered. Although univariate analysis results demonstrated previous pneumococcal vaccination was associated with a significant increase in risk of recurrence in those aged 15 years or more, these recurrent cases all occurred in Indigenous Australians, and previous vaccination was found to be non-significant during multivariate modelling.

From 2012 to 2015, 60% of recurrent cases were potentially preventable through use of 13vPCV (33%) or 23vPPV (27%). This was a decrease from the 70% of recurrent cases caused by the same serotypes from 2005 to 2011. Changes in vaccine preventability of recurrent cases therefore need to be monitored due to ongoing pneumococcal serotype replacement. Serotype distribution data are required to inform vaccine recommendations to prevent recurrent disease, as we are likely to see continued decreased incidence of 13vPCV serotypes and the potential for increased numbers of cases due to the extra serotypes contained in 23vPPV.

While our study has identified an increased risk of recurrent IPD in certain groups, there are inherent limitations in using notification data for this type of analysis. Firstly, there is potential for misclassification of primary cases of IPD in individuals who had IPD prior to the study period, interstate, or overseas, or an individual with primary IPD in our study may have subsequently experienced a recurrent episode out of state. This type of misclassification would lead to an underestimate of recurrent case count and rate, leading to our estimate representing a minimum estimate of the true value. Secondly, individuals in our study who died outside of Queensland would not be identified, and continue to contribute person-years at risk of disease. Again, an error of this nature would lead to our estimate being a minimum estimate of the recurrence rate. Thirdly, completeness of notification data and differences in reporting of risk factors for children and adults is a source of potential misclassification. Data completeness might have contributed to our finding that only half of those with recurrent disease had any risk factor identified, considerably lower than reported elsewhere.[1,25,28,29] While lack of risk factor completeness could affect the estimated crude rates and proportional hazards analyses for certain variables, it would not change the primary outcome of disease recurrence. Lastly, estimates of pneumococcal vaccination coverage may be an underestimate, particularly in the adult population. Transitioning to the Australian Immunisation Register, which will include immunisation data for all ages, should improve the accuracy of future studies in estimating vaccination coverage in the adult population.

Conclusions

In response to the high numbers of nationally reported vaccine failures, ATAGI has recently proposed changing to a 2+1 13vPCV schedule.[63] Our experience of breakthrough disease in Queensland supports this proposed change, with the likely benefits of providing a booster dose to outweigh any potential harm from the reduced number of primary course doses. However, one group neglected in the proposed schedule change are those aged 1–4 years who have received a 3+0 course, and are therefore at ongoing risk of breakthrough disease. A targeted catch-up campaign with one 13vPCV booster dose for children in the second

year of life would mitigate those likely to be at highest risk for future breakthrough disease. Ongoing monitoring of breakthrough disease and serotype distribution will be necessary to evaluate the impact of any schedule change.

The absence of previous IPD as an identified at-risk group in national immunisation guidelines likely contributes to the low vaccination coverage and the persistently elevated rates of recurrent disease. With a majority of recurrent cases potentially vaccine-preventable based on infecting serotypes, we recommend that global immunisation guidelines specifically identify any episode of prior IPD as requiring pneumococcal vaccination.

References

1. King MD, Whitney CG, Parekh F, Farley MM. Recurrent invasive pneumococcal disease: a population-based assessment. *Clin Infect Dis* 2003;37(8):1029-36.

2. O'Brien KL, Wolfson LJ, Watt JP, Henkle E, Deloria-Knoll M, McCall N, et al. Burden of disease caused by *Streptococcus pneumoniae* in children younger than 5 years: global estimates. *Lancet* 2009;374(9693):893-902.

3. Earle K, Williams S. Burden of pneumococcal disease in adults aged 65 years and older: an Australian perspective. *Pneumonia* 2016;8(1):9.

4. Drijkoningen JJC, Rohde GGU. Pneumococcal infection in adults: burden of disease. *Clin Microbiol Infect* 2014;20:45-51.

5. World Health Organization. *Estimated Hib and pneumococcal deaths for children under 5 years of age, 2008* [Internet]. 2013 [cited 2017 Sept 1]. Available from: http://www.who.int/immunization/monitoring_surveillance/burden/estimates/Pneumo_hib/en/

6. Toms C, de Kluyver R. Invasive pneumococcal disease in Australia, 2011 and 2012. *Commun Dis Intell Q Rep* 2016;40(2):E267.

7. Australian Technical Advisory Group on Immunisation. *The Australian Immunisation Handbook (10th ed): 4.13 Pneumococcal disease*. Canberra (AUST): Australian Government Department of Health; 2017.

8. Williams SR, Mernagh PJ, Lee MH, Tan JT. Changing epidemiology of invasive pneumococcal disease in Australian children after introduction of a 7-valent pneumococcal conjugate vaccine. *Med J Aust* 2011;194(3):116.

9. National Centre for Immunisation Research and Surveillance. *History of vaccination in Australia: pneumocccal* [Internet]. 2015 [cited 2017 Aug

2]. Available from: http://www.ncirs.edu.au/provider-resources/vaccination-history/

10. Hull BP, Hendry A, Dey A, Beard F, Brotherton JM, McIntyre PB. Immunisation coverage annual report, 2014. *Commun Dis Intell Q Rep* 2017;41(1):E68-90.

11. Australian Government Department of Health. *National Notifiable Diseases Surveillance System data* [Internet]. 2017 [cited 2017 Aug 2]. Available from: http://www9.health.gov.au/cda/source/cda-index.cfm

12. Waight PA, Andrews NJ, Ladhani SN, Sheppard CL, Slack MP, Miller E. Effect of the 13-valent pneumococcal conjugate vaccine on invasive pneumococcal disease in England and Wales 4 years after its introduction: an observational cohort study. *Lancet Infect Dis* 2015;15(5):535-43.

13. Miller E, Andrews NJ, Waight PA, Slack MP, George RC. Herd immunity and serotype replacement 4 years after seven-valent pneumococcal conjugate vaccination in England and Wales: an observational cohort study. *Lancet Infect Dis* 2011;11(10):760-8.

14. Loo JD, Conklin L, Fleming-Dutra KE, Knoll MD, Park DE, Kirk J, et al. Systematic review of the indirect effect of pneumococcal conjugate vaccine dosing schedules on pneumococcal disease and colonization. *Pediatr Infect Dis J* 2014;33(S2):S161-71.

15. Whitney CG, Goldblatt D, O'Brien KL. Dosing schedules for pneumococcal conjugate vaccine: considerations for policy makers. *Pediatr Infect Dis J* 2014;33(S2):S172-81.

16. Black S, Shinefield H, Fireman B, Lewis E, Ray P, Hansen JR, et al. Efficacy, safety and immunogenicity of heptavalent pneumococcal conjugate vaccine in children. *Pediatr Infect Dis J* 2000;19(3):187-95.

17. Knoll MD, Park DE, Johnson TS, Chandir S, Nonyane BAS, Conklin L, et al. Systematic review of the effect of pneumococcal conjugate vaccine

dosing schedules on immunogenicity. *Pediatr Infect Dis J* 2014;33(S2):S119-29.

18. Conklin L, Loo JD, Kirk J, Fleming-Dutra KE, Deloria Knoll M, Park DE, et al. Systematic review of the effect of pneumococcal conjugate vaccine dosing schedules on vaccine-type invasive pneumococcal disease among young children. *Pediatr Infect Dis J* 2014;33(S2):S109-18.

19. Fleming-Dutra KE, Conklin L, Loo JD, Knoll MD, Park DE, Kirk J, et al. Systematic review of the effect of pneumococcal conjugate vaccine dosing schedules on vaccine-type nasopharyngeal carriage. *Pediatr Infect Dis J* 2014;33(S2):S152-60.

20. Sanz J, Rodríguez-Avial I, Ríos E, Ramos B, Cercenado E. Recurrent pneumococcal invasive disease in the Region of Madrid during a five-year period. *Infection* 2014;42(3):475-83.

21. Mason EOJP, Wald ERMD, Tan TQMD, Schutze GEMD, Bradley JSMD, Barson WJMD, et al. Recurrent systemic pneumococcal disease in children. *Pediatr Infect Dis J* 2007;26(6):480-4.

22. Alsina L, Basteiro MG, de Paz HD, Iñigo M, de Sevilla MF, Triviño M, et al. Recurrent invasive pneumococcal disease in children: underlying clinical conditions, and immunological and microbiological characteristics. *PLoS One* 2015;10(3):e0118848.

23. Turett GS, Blum S, Telzak EE. Recurrent pneumococcal bacteremia: risk factors and outcomes. *Arch Intern Med* 2001;161(17):2141-4.

24. Mufson MA, Hao JB, Stanek RJ, Norton NB. Clinical features of patients with recurrent invasive *Streptococcus pneumoniae* disease. *Am J Med Sci* 2012;343(4):303-9.

25. Einarsdóttir HM, Erlendsdóttir H, Kristinsson KG, Gottfredsson M. Nationwide study of recurrent invasive pneumococcal infections in a population with a low prevalence of human immunodeficiency virus infection. *Clin Microbiol Infect* 2005;11(9):744-9.

26. Rodríguez-Créixems M, Muñoz P, Miranda E, Peláez T, Alonso R, Bouza E. Recurrent pneumococcal bacteremia: a warning of immunodeficiency. *Arch Intern Med* 1996;156(13):1429-34.

27. Orlicek SL, Herrod HG, Leggiadro RJ, Luedtke G, English BK. Repeated invasive pneumococcal infections in young children without apparent underlying immunodeficiency. *J Pediatr* 1997;130(2):284-8.

28. Font B, Lliminana C, Fontanals D, Pineda V, Segura F. Eleven-year study of recurrent pneumococcal bacteremia. *Eur J Clin Microbiol Infect Dis* 2001;20(9):636-8.

29. Coccia MR, Facklam RR, Saravolatz LD, Manzor O. Recurrent pneumococcal bacteremia: 34 episodes in 15 patients. *Clin Infect Dis* 1998;26(4):982-5.

30. Lee W, Austrian R, Weiser JN. Recurrent pneumococcal bacteremia in normal children. *Pediatr Infect Dis J* 1994;13(3):231-2.

31. Australian Government Department of Health. *Pneumococcal disease (invasive) case definition* [Internet]. 2004 [cited 2016 Oct 6]. Available from: http://www.health.gov.au/internet/main/publishing.nsf/content/cda-surveil-nndss-casedefs-cd_pnuemo.htm

32. Hull B, Lawrence G, MacIntyre C, Mcintyre P. Estimating immunisation coverage: is the'third dose assumption'still valid? *Commun Dis Intell Q Rep* 2003;27(3):357-61.

33. Australian Bureau of Statistics. *3101.0 - Australian Demographic Statistics, Sep 2015: Table 53. Estimated Resident Population By Single Year Of Age, Queensland* [Internet]. 2016 [cited 2016 May 23]. Available from: http://www.abs.gov.au/AUSSTATS/abs@.nsf/DetailsPage/3101.0Sep%202015?OpenDocument

34. Hull B, Deeks S, Menzies R, McIntyre P. Immunisation coverage annual report, 2007. *Commun Dis Intell Q Rep* 2009;33(2):170-87.

35. Hendry A. Australian childhood immunisation coverage, 1 July to 30 June cohort, assessed as at 30 September 2015. *Commun Dis Intell Q Rep* 2016;40(1):E177-8.

36. Hendry A. Australian childhood immunisation coverage, 1 July 2015 and 30 June 2016 cohort, assessed as at 30 September 2016. *Commun Dis Intell Q Rep* 2017;41(1):E106-8.

37. Ward KF, Trent M, Hull BP, Quinn HE, Dey A, Menzies RI. Evaluating the implementation of the 13-valent pneumococcal vaccine supplementary dose program in Australian primary health care settings. *BMC Health Serv Res* 2015;15:109.

38. Australian Bureau of Statistics. *3238.0.55.001 - Experimental estimates of Aboriginal and Torres Strait Islander Australians, Jun 2006: experimental estimated resident Australian Indigenous and non-Indigenous population, state and territories* [Internet]. 2008 [cited 2017 Aug 17]. Available from: http://www.abs.gov.au/AUSSTATS/abs@.nsf/DetailsPage/3238.0.55.001Jun%202006?OpenDocument

39. Jayasinghe S, Menzies R, Chiu C, Toms C, Blyth CC, Krause V, et al. Long-term impact of a "3 + 0" schedule for 7- and 13-valent pneumococcal conjugate vaccines on invasive pneumococcal disease in Australia, 2002–2014. *Clin Infect Dis* 2017;64(2):175-83.

40. Oligbu G, Hsia Y, Folgori L, Collins S, Ladhani S. Pneumococcal conjugate vaccine failure in children: a systematic review of the literature. *Vaccine* 2016;34(50):6126-32.

41. Oligbu G, Collins S, Andrews N, Sheppard CL, Fry NK, Slack MP, et al. Characteristics and serotype distribution of childhood cases of invasive pneumococcal disease following pneumococcal conjugate vaccination in England and Wales, 2006–2014. *Clin Infect Dis* 2017;65(7):1191-8.

42. Almeida AF, Sobrinho-Simões J, Ferraz C, Nunes T, Vaz L. Pneumococcal pneumonia vaccine breakthroughs and failures after 13-valent pneumococcal conjugated vaccine. *Eur J Public Health* 2016;26(5):887-9.

43. Andrews NJ, Waight PA, Burbidge P, Pearce E, Roalfe L, Zancolli M, et al. Serotype-specific effectiveness and correlates of protection for the 13-valent pneumococcal conjugate vaccine: a postlicensure indirect cohort study. *Lancet Infect Dis* 2014;14(9):839-46.

44. Miller E, Andrews NJ, Waight PA, Slack MP, George RC. Effectiveness of the new serotypes in the 13-valent pneumococcal conjugate vaccine. *Vaccine* 2011;29(49):9127-31.

45. Domínguez Á, Ciruela P, Hernández S, García-García JJ, Soldevila N, Izquierdo C, et al. Effectiveness of the 13-valent pneumococcal conjugate vaccine in preventing invasive pneumococcal disease in children aged 7-59 months: a matched case-control study. *PLoS One* 2017;12(8):e0183191.

46. Moore MR, Link-Gelles R, Schaffner W, Lynfield R. Effectiveness of 13-valent pneumococcal conjugate vaccine for prevention of invasive pneumococcal disease in children in the USA: a matched case-control study. *Lancet Respir Med* 2017;4(5):399-406.

47. Balsells E, Guillot L, Nair H, Kyaw MH. Serotype distribution of *Streptococcus pneumoniae* causing invasive disease in children in the post-PCV era: a systematic review and meta-analysis. *PLoS One* 2017;12(5):e0177113.

48. Dagan R, Patterson S, Juergens C, Greenberg D, Givon-Lavi N, Porat N, et al. Comparative immunogenicity and efficacy of 13-valent and 7-valent pneumococcal conjugate vaccine in reducing nasopharyngeal colonization: a randomized double-blind trial. *Clin Infect Dis* 2013;57(7):952-62.

49. Grant LR, O'Brien SE, Burbidge P, Haston M, Zancolli M, Cowell L, et al. Comparative immunogenicity of 7 and 13-valent pneumococcal conjugate vaccines and the development of functional antibodies to cross-reactive serotypes. *PLoS One* 2013;8(9):e74906.

50. Givon-Lavi N, Greenberg D, Dagan R. Immunogenicity of alternative regimens of the conjugated 7-valent pneumococcal vaccine: a randomized controlled trial. *Pediatr Infect Dis J* 2010;29(8):756-62.

51. Klugman KP, Madhi SA, Huebner RE, Kohberger R, Mbelle N, Pierce N. A trial of a 9-valent pneumococcal conjugate vaccine in children with and those without HIV infection. *N Engl J Med* 2003;349(14):1341-8.

52. Rodgers GL, Esposito S, Principi N, Gutierrez-Brito M, Diez-Domingo J, Pollard AJ, et al. Immune response to 13-valent pneumococcal conjugate vaccine with a reduced dosing schedule. *Vaccine* 2013;31(42):4765-74.

53. Pennington K, Glynn-Robinson A, Toms C. Invasive pneumococcal disease surveillance, 1 January to 31 March 2016. *Commun Dis Intell Q Rep* 2016;40(2):E308-12.

54. Glynn-Robinson A, Pennington K, Toms C. Invasive pneumococcal disease surveillance, 1 April to 30 June 2016. *Commun Dis Intell Q Rep* 2016;40(4):E564-E8.

55. Corvisy R, Hood J, Group EIPDSW, Australia CDN. Invasive pneumococcal disease surveillance, 1 July to 30 September 2016. *Commun Dis Intell Q Rep* 2016;40(4):E569.

56. Pennington K. Invasive pneumococcal disease surveillance, 1 October to 31 December 2016. *Commun Dis Intell Q Rep* 2017;41(1):E114-E9.

57. Wagenvoort GHJ, Vlaminckx BJM, van Kessel DA, Geever RCL, de Jong BAW, Grutters JC, et al. Pneumococcal conjugate vaccination response in patients after community-acquired pneumonia, differences in patients with *S. pneumoniae* versus other pathogens. *Vaccine* 2017;35(37):4886-95.

58. Spleen Australia. *Medical guidelines for individuals with asplenia or hyposplenism* [Internet]. Melbourne (AUST): Spleen Australia, Alfred Health; 2016 [cited 2017 Sept 2]. Available from: https://spleen.org.au/VSR/files/RECOMMENDATIONS_Spleen_Registry_p.pdf

59. Spleen Australia. *Recommendations for the prevention of infection in patients with asplenia (splenectomy) or hyposplenism aged over 18 years* [Internet]. Melbourne (AUST): Spleen Australia, Alfred Health; 2016 [cited 2017 Sept 2]. Available from: https://spleen.org.au/VSR/files/RECOMMENDATIONS_Spleen_Registry.pdf

60. Australian Technical Advisory Group on Immunisation. *The Australian Immunisation Handbook (10th ed): 2.1 Pre-vaccination*. Canberra (AUS): Australian Government Department of Health; 2015.

61. Gaschignard J, Levy C, Chrabieh M, Boisson B, Bost-Bru C, Dauger S, et al. Invasive pneumococcal disease in children can reveal a primary immunodeficiency. *Clin Infect Dis* 2014;59(2):244-51.

62. Moberley S, Krause V, Cook H, Mulholland K, Carapetis J, Torzillo P, et al. Failure to vaccinate or failure of vaccine? Effectiveness of the 23-valent pneumococcal polysaccharide vaccine program in Indigenous adults in the Northern Territory of Australia. *Vaccine* 2010;28(11):2296-301.

63. Australian Government Department of Health. *Proposed changes to the infant pneumococcal vaccination schedule recommendations* [Internet]. 2017 [cited 2017 Sept 2]. Available from: https://consultations.health.gov.au/ohp-immunisation-branch/infant-pneumococcal-vaccination-schedule-recommend/

Appendix A—Letter to ATAGI

ATAGI Secretariat
Department of Health
Immunisation Branch
GPO Box 9848 - MDP 13
CANBERRA ACT 2601

ATAGI.Secretariat@health.gov.au

25 January 2017

Dear ATAGI Secretariat

Re: Previous invasive pneumococcal disease (IPD) as a high-risk group for future disease

We understand that the Pneumococcal Disease chapter of the Australian Immunisation Handbook is currently being reviewed by the Australian Technical Advisory Group on Immunisation (ATAGI) pneumococcal working group. In recent months, we have been analysing IPD notification data in Queensland and believe that some of our findings related to high-risk groups are relevant to the current review.

There are specific high-risk groups for IPD, of which some are either funded or recommended to receive protective doses of 13-valent pneumococcal conjugate vaccine (13vPCV), 23-valent pneumococcal polysaccharide vaccine (23vPPV), or both. One group that is currently neither funded nor recommended to receive pneumococcal vaccination is those who have had a previous episode of IPD. In the literature, recurrent IPD is often reported as a proportion (typically <2%) of overall IPD cases, with little emphasis on the actual rate of recurrent disease in individuals after they experience an initial episode of IPD. Limited overseas evidence has found that this group experiences future episodes of IPD at a rate that is 50 times the rate of IPD in the general population.

Due to the lack of local evidence regarding the risk of recurrent IPD, we reviewed IPD notifications in Queensland from 1997 to 2015 and estimated the rate of recurrent disease using time-to-event analysis. Additionally, we reviewed the

causative serotypes identified in cases of recurrent disease to assess the potential for preventing these through targeted pneumococcal vaccination.

From 1997 to 2015, there were 6,057 IPD notifications in Queensland, of which 120 (2.0%) were recurrent episodes in 102 individuals. Those surviving >14 days after their initial episode of IPD contributed 45,394 person-years at risk of recurrent disease to our analysis.

The overall rate of primary IPD during the study period was 7.8 per 100,000 population per year, while the rate of recurrent disease was 264.4 per 100,000 person-years, approximately 35 times the rate of IPD in the general population (Table).

Since 2012, the rate of recurrent IPD (280.4 per 100,000 person-years) is 50 times the rate of IPD in the general population (5.6 per 100,000 population per year). The median time between the first and second episodes was 20 months (range: 27 days–12 years, mean: 31 months). The rate of further (≥3 episodes) IPD recurrence was 3,592.7 per 100,000 person-years.

Among Aboriginal and Torres Strait Islander people, the rate of recurrent IPD (991.1 per 100,000 person-years) is more than four times the rate of recurrent IPD in the non-Indigenous population (215.5 per 100,000 person-years), and over 100 times greater than the rate of primary IPD in the general population.

The proportion of primary and recurrent IPD cases presenting with meningitis, bacteraemia, and bacteraemic pneumonia were similar. While the rate point estimate of future episodes following an initial episode of meningitis IPD was nearly double that after an initial episode of bacteraemic or pneumonic IPD, the difference was not significant.

We found that 48% of individuals with recurrent IPD had no risk factor identified at the time of their initial episode, compared to 58% of those with single-episode-only IPD. Only 30% of all individuals having a second episode of IPD had a vaccination record in the Queensland vaccination register of having received a pneumococcal vaccine (7vPCV, 13vPCV, or 23vPPV). Among those who had any risk factor identified through surveillance at the time of their initial IPD episode, the rate of recurrence was 549.1 per 100,000 person-years, compared to 168.0 per 100,000 person-years in those who had no identified risk factor identified at this time.

Overall, 70% of recurrent episodes were potentially vaccine-preventable from 2001–2015, with 60% of recurrent episodes being caused by vaccine-preventable serotypes since 2012. While the rate of recurrent IPD episodes caused by non-vaccine pneumococcal serotypes has increased (Figure), the overall rate of potentially vaccine-preventable IPD episodes remains greater.

Our findings have highlighted that those with previous IPD are at significantly elevated risk of future IPD, a risk that disproportionately affects Aboriginal and Torres Strait Islander people. While the rate of recurrence was higher amongst individuals with known risk factors for IPD, the risk remained over 20 times higher than the general population in those with no identified risk factor at the time of their first episode.

We suggest that given this evidence, the working group should consider adding previous IPD as a distinct at-risk category, and those with previous IPD should be specifically recommended to receive pneumococcal vaccination in Australia. The inclusion of this group in the current Handbook revision would be timely.

Additionally, we have received ethics approval for a national study to estimate recurrent IPD rates in all Australian states and territories, and are currently in the process of acquiring the data from the National Notifiable Diseases Surveillance System through CDNA.

Please contact us if you would like further details of our analyses of Queensland data. We are happy to provide updates once the national dataset has been received and analysed.

Kind Regards

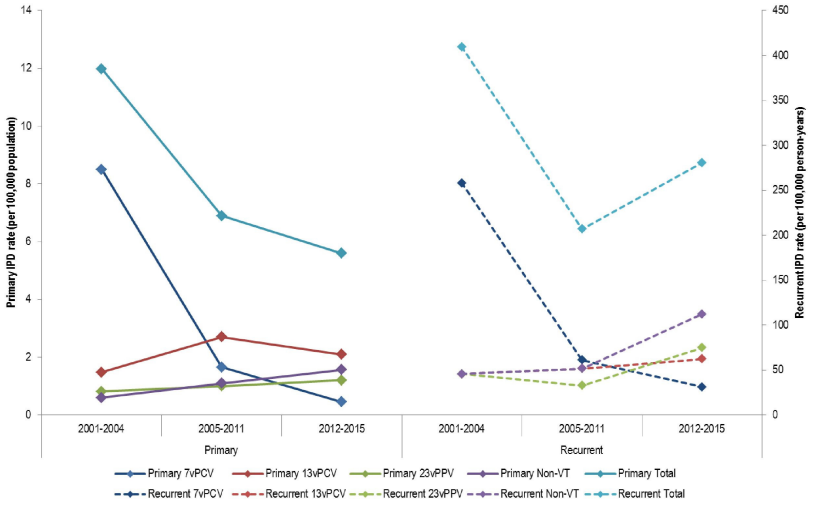
Dr Jonathan Malo
Epidemiology Registrar,
Epidemiology & Research Unit
Communicable Diseases Branch,
Queensland Health
e. jonathan.malo@health.qld.gov.au
p: (07) 3328 9178

Dr Stephen Lambert
Medical Director,
Epidemiology & Research Unit
Communicable Diseases Branch,
Queensland Health
e: stephen.lambert@health.qld.gov.au
m: 0405 974 555

Table—Recurrent and primary invasive pneumococcal disease rates by age group, sex, Indigenous status, clinical syndrome, time period, and identified risk factor, Queensland, Australia, 1997–2015

	Recurrent IPD			Primary IPD	
	No. (%)[a]	Rate (per 100,000 person-years)	(95% CI)	No. (%)[a]	Rate (per 100,000 per year)
Age group (years)					
<5	8 (6.7)	166.1	(83.1–332.1)	1596 (26.8)	30.6
5 to <15	12 (10.0)	89.6	(50.9–157.8)	327 (5.5)	3.1
15 to <50	51 (42.5)	376.9	(286.4–495.9)	1553 (26.1)	4.1
50 to <65	27 (22.5)	465.8	(319.5–679.3)	1016 (17.1)	7.7
≥65	22 (18.3)	280.5	(184.7–426.0)	1462 (24.6)	15.3
Sex					
Male	64 (53.3)	253.4	(198.3–323.7)	3294 (55.3)	8.6
Female	56 (46.7)	278.4	(214.2–361.7)	2660 (44.7)	6.9
Indigenous status					
Indigenous	54 (45.0)	991.1	(759.1–1,279.4)	756 (12.7)	23.9
Non-Indigenous	66 (55.0)	215.5	(168.3–275.8)	5199 (87.3)	6.8
Clinical syndrome[b]					
Bacteraemia	33 (27.5)	339.98	(229.7–503.2)	989 (16.6)	1.3
Meningitis	6 (5.0)	670.14	(348.7–1288.0)	222 (3.7)	0.3
Pneumonia	35 (29.2)	359.8	(255.8–506.1)	1769 (29.7)	2.3
Time period					
1997–2000	4 (3.3)	268.8	(100.9–716.2)	1103 (18.5)	8.0
2001–2004	27 (22.5)	409.4	(280.8–597.0)	1772 (29.8)	12.0
2005–2011	44 (36.7)	206.6	(153.8–277.7)	2033 (34.1)	6.9
2012–2015	45 (37.5)	280.4	(209.3–375.5)	1047 (17.6)	5.6
1997–2015	120 (100.0)	264.4	(221.0–316.1)	5955 (100.0)	7.8
Identified risk factor at time of initial episode[c]					
No risk factor	49 (48.0)	—	—	3391 (57.9)	—
Chronic disease	30 (29.4)	—	—	956 (16.3)	—
Current smoker	21 (20.6)	—	—	478 (8.2)	—
Excess alcohol consumption	14 (13.7)	—	—	304 (5.2)	—
Aged ≥65 years, non-Indigenous	13 (12.7)	—	—	1402 (24.0)	—
Immunosuppression	10 (9.8)	—	—	324 (5.5)	—
Diabetes	8 (7.8)	—	—	181 (3.1)	—
Aged ≥50 years, Indigenous	6 (5.9)	—	—	147 (2.5)	—
Prematurity (<37 weeks)	3 (2.9)	—	—	109 (1.9)	—
Cardiac disease	2 (2.0)	—	—	191 (3.3)	—
Asplenia	2 (2.0)	—	—	53 (0.9)	—
Pulmonary disease	1 (1.0)	—	—	135 (2.3)	—

[a] Percentages calculated using denominators of 120 (recurrent) and 5,955 (primary), except as noted in c
[b] Recurrent episodes and recurrent rates following an initial episode of either bacteraemia, meningitis or pneumonia
[c] Percentages calculated using denominators of 102 individuals (recurrent) and 5,853 (single-episode-only)



Figure—Rates of recurrent and primary invasive pneumococcal disease by time period and infecting serotype according to pneumococcal vaccine serogroup, Queensland, Australia, 2001–2015. (IPD, invasive pneumococcal disease; 7vPCV, 7-valent pneumococcal conjugate vaccine serotypes; 13vPCV, 13-valent pneumococcal conjugate vaccine serotypes excluding 7vPCV serotypes, 23vPPV, 23-valent pneumococcal polysaccharide vaccine serotypes excluding 13vPCV serotypes; Non-VT, non-vaccine type serotypes)

(This page lacks meaning and purpose)

(This page is not intended to communicate anything noteworthy)

V

Lessons from the field and additional teaching activities

Lessons from the field

Background

One of the core MAE requirements is teaching and participating in Lessons from the Field (LFF) activities. One of the skills I developed as part of my invasive pneumococcal disease project (Chapter IV) was working with data that has multiple records per subject in Stata. I decided this was a valuable skill to share with others and would be the focus of my LFF.

Lessons learned

The most challenging aspect of preparing the LFF was, given a wide range of backgrounds and skills, ensuring the exercise was valuable to each of the participants. I have a greater appreciation for the difficulty involved with this aspect of the teaching process, and have also been able to reflect further on suitable teaching strategies to achieve this outcome.

Additional teaching activities

Background

I was involved in additional teaching experiences during the time of my MAE placement, which included:

- participating in teaching one of the sessions during POPH8916 Outbreak Investigation subject for first-year MAE scholars.
- coordinating a teaching session titled “Epi Cranium” for first-year MAE scholars with fellow-MAE scholar, Rose Wright, that focused on building trust and rapport within the first-year cohort.
- training local staff in data collection and data entry processes during as part of my WHO consultancy in the Republic of the Marshall Islands (Chapter V).
- responding to ad hoc requests from fellow-MAE scholars for assistance and teaching with Stata commands.
- teaching fellow public health medicine trainees epidemiological concepts in preparation for the Australasian Faculty of Public Health Medicine final oral examination.

Lessons learned

The range of teaching experiences and audiences has been valuable in my development as an educator. Developing teaching materials has also caused me to reflect further on my own learning style and process. While I would often choose to approach teaching in a way that suits my personal learning style, I now give further thought to accommodating other learning styles and how the overall learning objectives might be met through various approaches to teaching.

Appendix A—Lessons from the Field

Lessons from the Field

Tips and tricks for working with multiple records per subject in Stata

Background

This lesson from the field (LFF) has been developed to assist other MAE scholars in working with datasets with multiple records per subject. The content of the LFF is based off my experience in working with datasets during my MAE placement as well as from previous experience in data management and analysis.

Learning objectives

Upon completion of the exercise, you should be able to:

- Discuss and recognise common issues that arise when working with datasets that have multiple records per subject
- Clean and prepare a dataset with multiple records per subject for analysis using the _n and _N functions, and the egen command with seq option in Stata
- Use scalars to store and recall relevant information from previous commands

Please complete tasks and questions related to the dataset and submit your responses and annotated .do file to Malo University (jonathanmalo@gmail.com) by **12:01 pm (i.e. noon) on Monday 21 November.**

Introduction to datasets with multiple records per subject

Datasets will often have multiple records (observations) per subject to describe discrete events, for instance, multiple admissions to hospital, multiple notifications, multiple records in a trauma registry, or multiple laboratory tests. This type of data is often referred to as 'record-level data' (as opposed to 'person-level data' where there is only one observation per person).

A sample of data with multiple records per subject is provided below:

id	onset_date	sex	dob
1	23/04/2005	M	12/08/1991
1	14/06/2006	M	12/08/1991
1	30/01/2009	M	12/08/1991
1	20/05/2010	M	12/08/1991
1	26/03/2012	M	12/08/1991
2	25/03/2006	F	21/07/1985
2	12/07/2008	F	21/07/1985
3	19/05/2007	M	26/04/1962
3	11/06/2009	M	26/04/1962
3	26/08/2012	M	26/04/1962

In the above example, we can see that there are 5 records for person id 1, 2 records for person id 2, and 3 records for person id 3. While small samples are easy to inspect visually, we don't have this luxury when dealing with larger datasets.

Some common questions to consider regarding cleaning and preparing record-level datasets for analysis:

- Are demographics or risk factors that don't change with time consistently coded across all observations within an individual (e.g. sex, date of birth, Indigenous status)? If they aren't consistently coded, what do you do with those observations (e.g. consider them erroneous and drop them)?

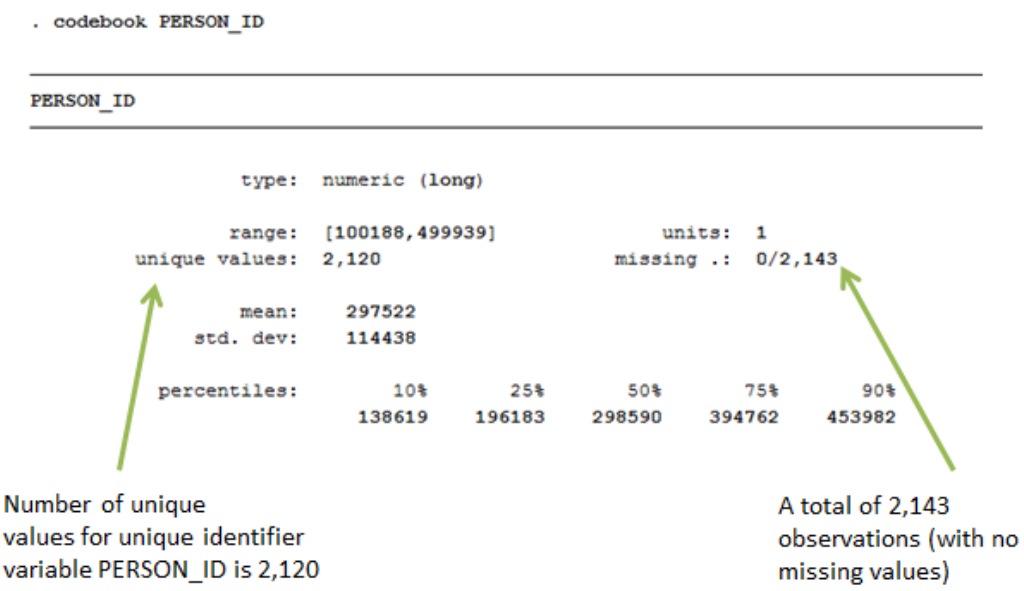
- How do you treat missing data for some fields (particularly risk factors) where they have been completed for previous observations in the same individual (e.g. presence of cardiac disease, smoking status)?
- Do all the date variables make sense (e.g. hospitalisation record after date of death, years between disease onset date and notification date)?
- What type of analysis are you going to perform on the data (e.g. survival analysis, descriptive)? We won't go into this much but is important to think about what you want your cleaned dataset to look like.

Preliminary Task 1. *Can you think of any other issues that you might encounter, or have already encountered when using datasets with multiple records per subject?*

Useful commands and functions when working with multiple records per subject

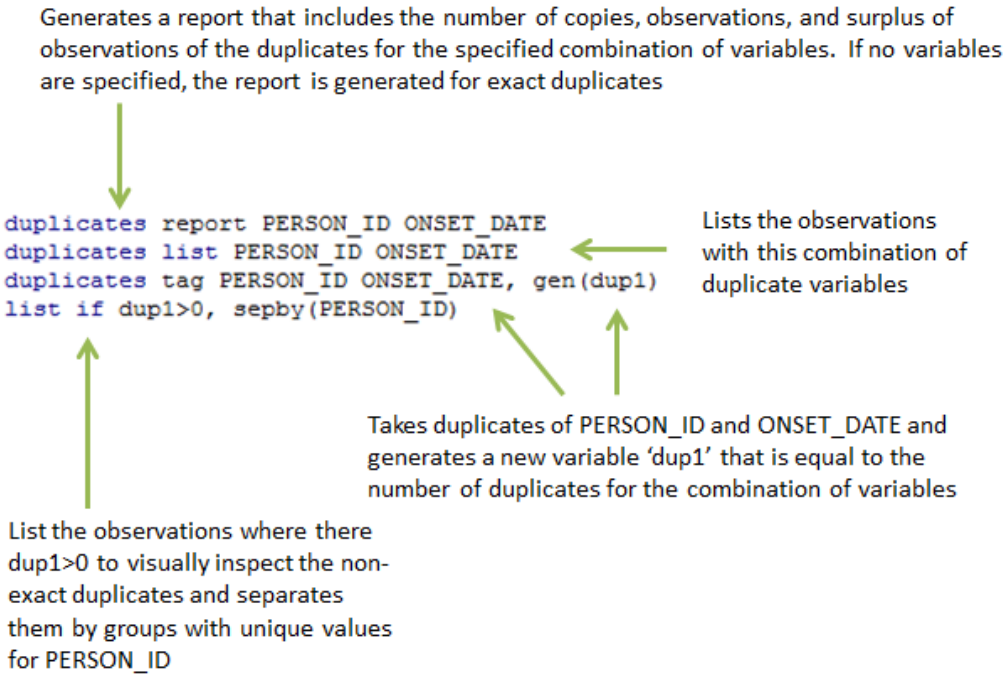
Thankfully, Stata has some useful ways to work with multiple record subject data so that we can work across observations to clean and prepare data for analysis. Brief explanations are provided for how these commands may be used, as well as hyperlinks to more extensive resources that I have found helpful.

codebook: Running the codebook command with the unique person identifier in your dataset is a quick way to check if there are multiple records per subject as the number of unique values are given, which can be compared to the total number of observations in the dataset. An example of the Stata output after running the codebook command on a unique person identifier variable is provided below:

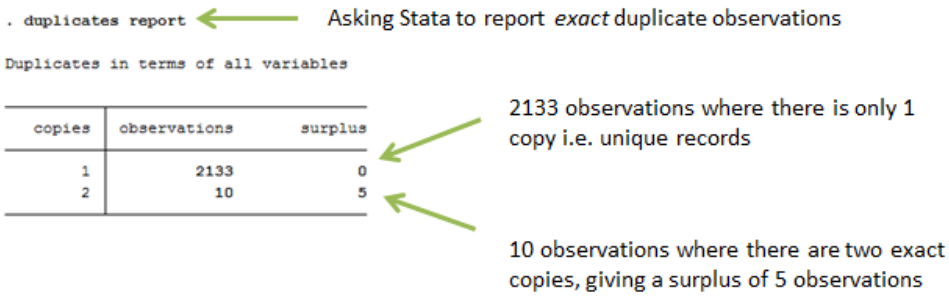


In the above example, we can see that the number of unique values for the unique person identifier variable PERSON_ID (=2,120) is less than the total number of observations in the dataset (=2,143). With no missing values, we can deduce that there are multiple records per subject in the dataset.

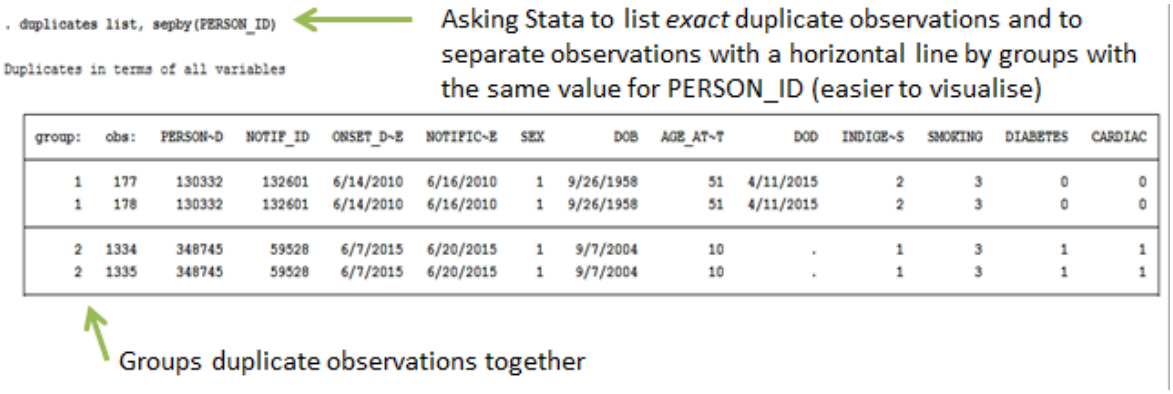
duplicates: It's important to check that multiple observations of the same event have not been recorded for an individual. With the duplicates command, we can check for exact duplicates, or partial duplicates using unique person identifiers combined with other variables such as dates and notification IDs. Below is an example of how we can use the duplicates command.



Below are examples of the Stata output after the duplicates report command and duplicates list:



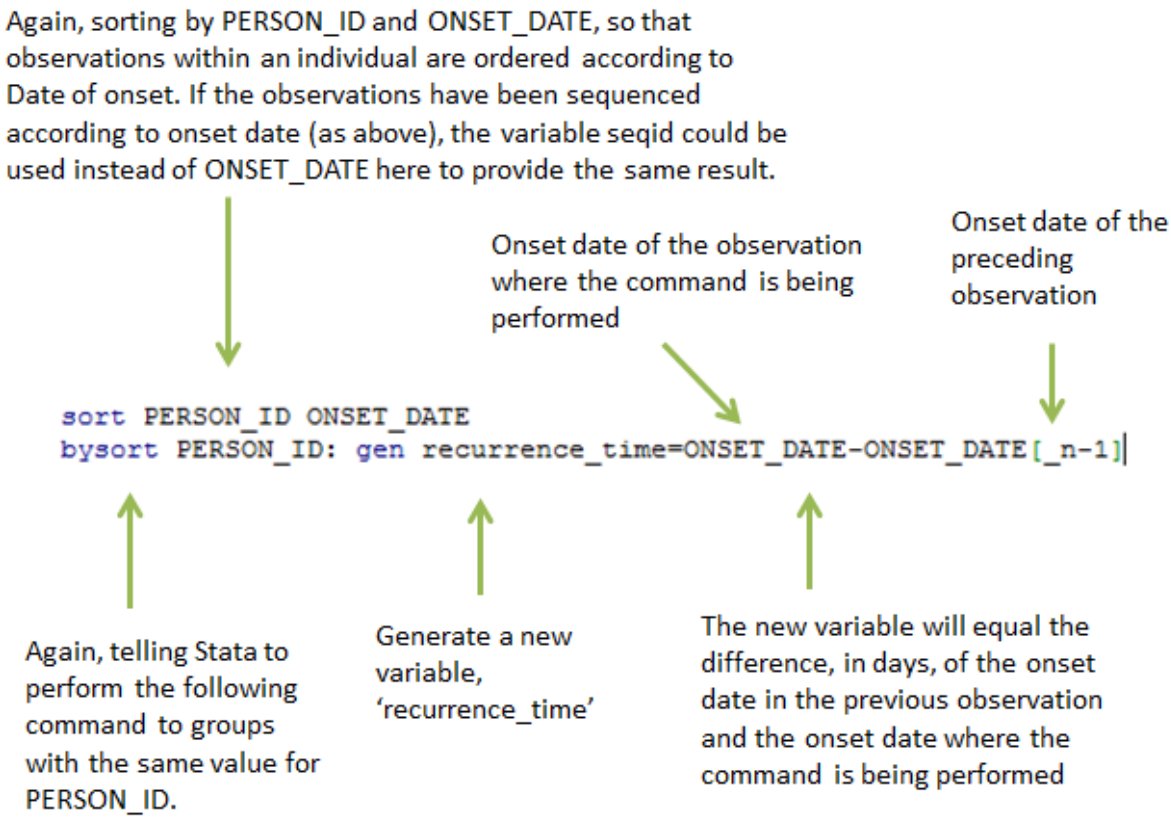
copies	observations	surplus
1	2133	0
2	10	5



group:	obs:	PERSON~D	NOTIF_ID	ONSET_D~E	NOTIFIC~E	SEX	DOB	AGE_AT~T	DOD	INDIGE~S	SMOKING	DIABETES	CARDIAC
1	177	130332	132601	6/14/2010	6/16/2010	1	9/26/1958	51	4/11/2015	2	3	0	0
1	178	130332	132601	6/14/2010	6/16/2010	1	9/26/1958	51	4/11/2015	2	3	0	0
2	1334	348745	59528	6/7/2015	6/20/2015	1	9/7/2004	10	.	1	3	1	1
2	1335	348745	59528	6/7/2015	6/20/2015	1	9/7/2004	10	.	1	3	1	1

Counting with _n and _N functions:

Frequently, we need to access information for an individual from an earlier or later observation. This often occurs when looking at time between observations or risk factors that have been recorded in previous observations. Using _n and _N functions with the gen command allow us to do this. _n refers to an observation within the dataset, and can be specified for within a person (or other variable), and _N refers to the last observation in a dataset, and can be specified for within a person (or other variable). When using _n, you can specify observations before (e.g. _n-1) or after (e.g. _n+1) the observation where the variable is being created. An example is provided below for using _n to calculate time between observations:

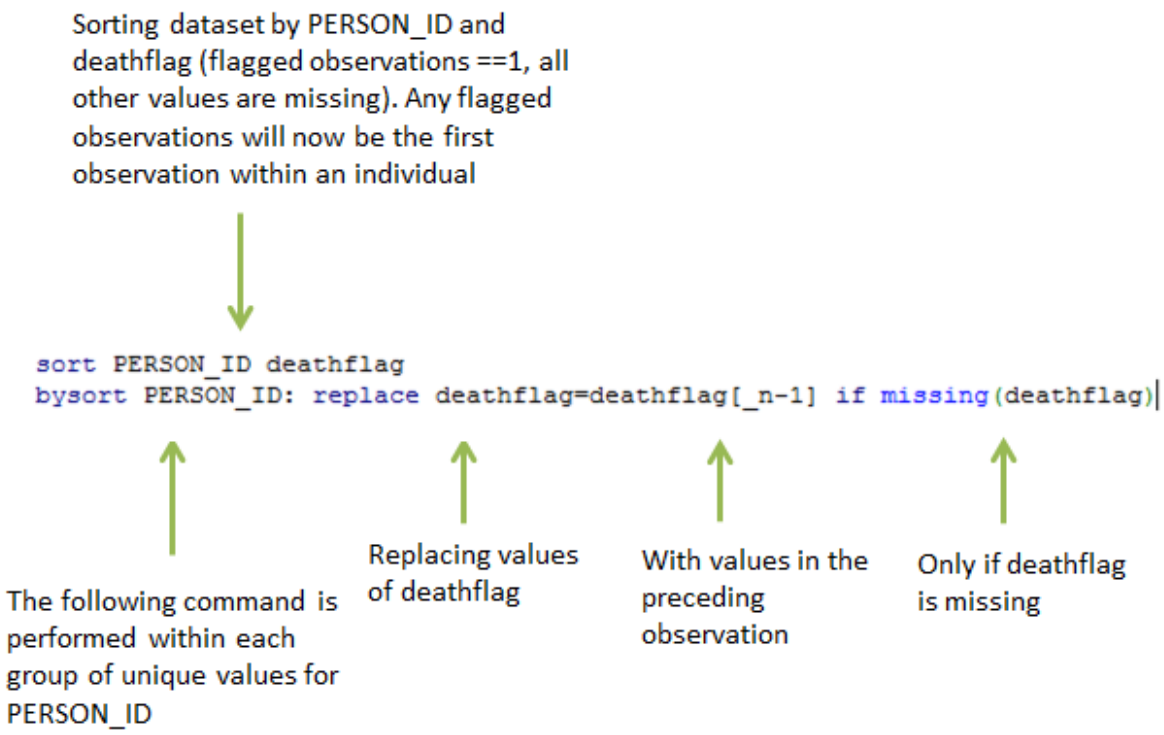


The above command would transform the data as we see here:

PERSON_ID	ONSET_DATE	recurrence_time
133535	31/03/2008	.
133535	17/12/2010	991
133535	6/06/2013	902
133535	31/03/2015	663

In the above example, we generate a new variable, 'recurrence_time', equal to the number of days between the preceding onset date and the onset date of the observation where the command is running, within each set of observations for a unique value of PERSON_ID. Stata will run through this command through the whole dataset. There is a missing value for the first observation of each individual, because there is no preceding observation within that individual to make a calculation. If we were interested in creating a variable based on the time until the *next* onset date (instead of from the previous), we would have specified [_n+1] in the command.

Combining the sort command with _n functions can be very useful when creating new variables that take on the same value for every observation within an individual (e.g. date of death, presence of a particular condition, flagging individuals for discrepancies with their observations etc.). Sorting a dataset by unique person identifier and a flagging variable (where flagged observations =1 and non-flagged observations are missing), arranges the dataset so you can 'carry' the value in the flagged variable to the other missing observations within an individual. An example is provided below where we have created a variable, deathflag, that is equal to 1 where an individual has a death recorded in an observation (date of death not missing), and we want to carry that value of 1 to all other observations within that individual. :



The above command would perform the following transformations to the dataset:

PERSON_ID	ONSET_DATE	DEATH_DATE	deathflag
133535	31/03/2008	.	.
133535	17/12/2010	.	.
133535	6/06/2013	.	.
133535	31/03/2015	4/04/2015	1

↓

PERSON_ID	ONSET_DATE	DEATH_DATE	deathflag
133535	31/03/2015	4/04/2015	1
133535	31/03/2008	.	.
133535	17/12/2010	.	.
133535	6/06/2013	.	.

↓

PERSON_ID	ONSET_DATE	DEATH_DATE	deathflag
133535	31/03/2015	4/04/2015	1
133535	31/03/2008	.	1
133535	17/12/2010	.	1
133535	6/06/2013	.	1

In the above example, because missing values in Stata take on a value of infinity and the sort command arranges observations in ascending order,

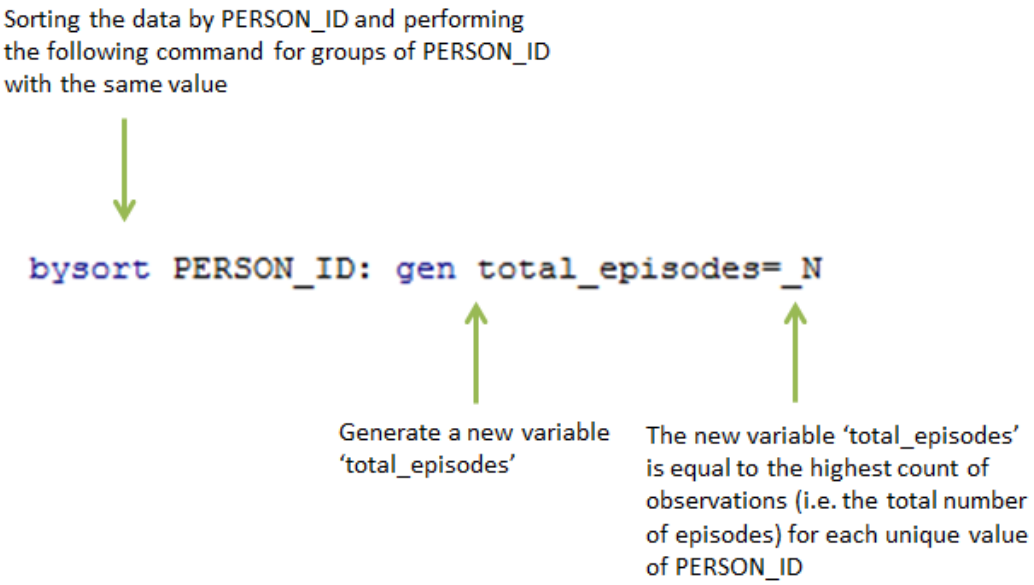
observations are then arranged according to PERSON_ID, with the observation with deathflag==1 at the top. All other observations with the same unique value for PERSON_ID will then take on the same value for deathflag. If an individual hasn't died and all of their observations for deathflag are missing, the values will all remain missing.

Preliminary Task 2. Imagine you are given a hospital record dataset (with multiple records per subject) that contains variables for a unique identifier (HOSPITAL_ID), discharge date (DISCHARGE_DATE), and admission date (ADMIT_DATE).

a) You want to create a variable (dis_to_admit) that is the time between the most recent discharge to the subsequent admission. Write the Stata code you would use to do this.

b) How would you interpret a value of <0 for dis_to_admit?

The _N function can be used to represent the highest count or last observation, either in the dataset or according to a defined group. This can be useful when we are interested in the total number of observations within an individual, or values from variables in their last observation. Two examples are provided below:



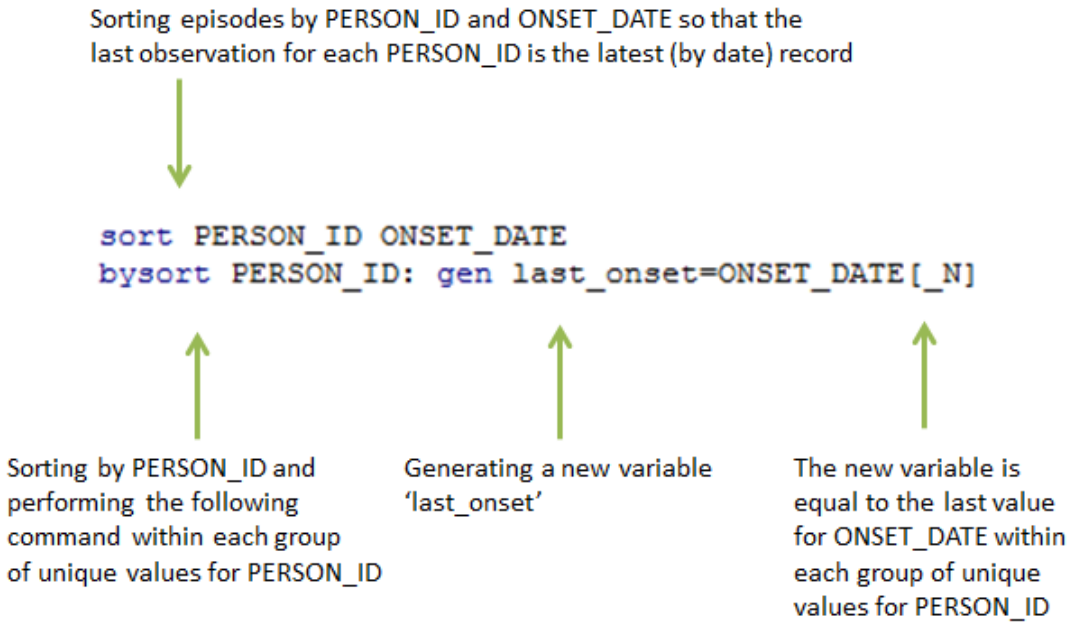
The above command would perform the following transformation of our dataset:

PERSON_ID	ONSET_DATE
133535	31/03/2015
133535	31/03/2008
133535	17/12/2010
133535	6/06/2013
146782	25/03/2006
146782	12/07/2008
198754	19/05/2007
198754	11/06/2009
198754	26/08/2012

PERSON_ID	ONSET_DATE	total_episodes
133535	31/03/2015	4
133535	31/03/2008	4
133535	17/12/2010	4
133535	6/06/2013	4
146782	25/03/2006	2
146782	12/07/2008	2
198754	19/05/2007	3
198754	11/06/2009	3
198754	26/08/2012	3

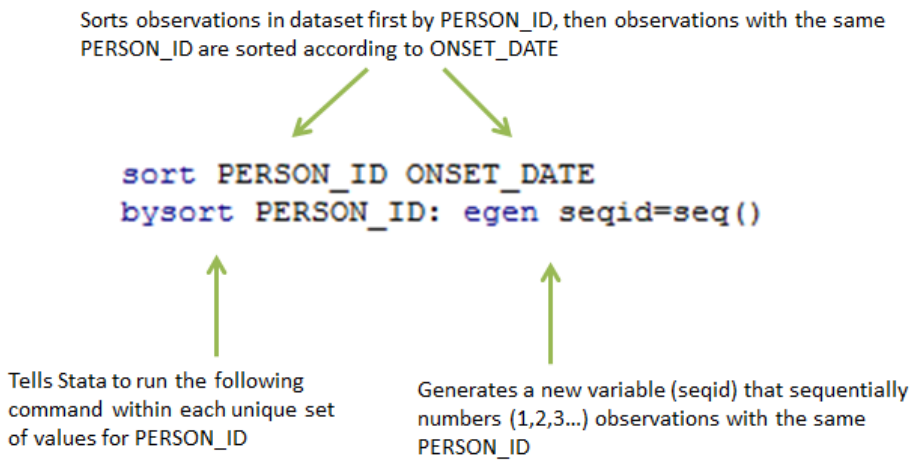
In the above examples, we see how we can use the _N function on its own to generate a variable for each observation within an individual that contains the total number of observations for that individual in a dataset.

In the example below, we use the _N function to specify a value from the last observation within an individual in our dataset:



The above command would perform the following transformation to our dataset:

egen with seq(): It is often useful to number the observations within an individual according to an order (often by date). We can do this using the egen command (a fancy version of the gen command to create new variables), or with the _n function. An example of how to do this is provided below:



The command above would perform the following transformation to our dataset:

PERSON_ID	ONSET_DATE
133535	31/03/2015
133535	31/03/2008
133535	17/12/2010
133535	6/06/2013
146782	25/03/2006
146782	12/07/2008
198754	19/05/2007
198754	11/06/2009
198754	26/08/2012

PERSON_ID	ONSET_DATE	seqid
133535	31/03/2008	1
133535	17/12/2010	2
133535	6/06/2013	3
133535	31/03/2015	4
146782	25/03/2006	1
146782	12/07/2008	2
198754	19/05/2007	1
198754	11/06/2009	2
198754	26/08/2012	3

In the above example, it is important to first order the dataset according to how we want the observations to be sequenced. If we did not specify to order according to ONSET_DATE after PERSON_ID, the egen command would have

sequenced the observations according to the order (or lack of) that already existed. Note that we could achieve the same result using the _n function and using the command below:

```
sort PERSON_ID ONSET_DATE
bysort PERSON_ID: gen seqid=_n
```

The egen with seq() command has more options that allows you to customise the sequence further.

Scalars (this is a bonus and useful for not just record-level data)

After running certain commands in Stata, values are temporarily stored as 'scalars' until the next command is run. The scalars that are temporarily stored vary according to the preceding command. These values can be recalled using the return list command (sometimes it is ereturn list, or sreturn list, depending on the preceding command. More information is in the hyperlink).' Scalars can also be defined manually if you have an external value you would like to store and use repeatedly (e.g. population size).

An example of using scalars after the sum command is provided below:

```
. sum AGE_AT_ONSET

    Variable |        Obs        Mean    Std. Dev.       Min        Max
-------------+---------------------------------------------------------
AGE_AT_ONSET |      6,086    38.73589    29.76193           0        101

. return list

scalars:
                  r(N) =  6086
              r(sum_w) =  6086
               r(mean) =  38.73588563917187
                r(Var) =  885.7725854685957
                 r(sd) =  29.76193181681249
               r(min) =  0
               r(max) =  101
               r(sum) =  235746.6
```

Asks Stata to list the scalars stored from the sum command

List of scalars stored temporarily from the sum command

In the above example, the listed scalars are available to include in subsequent commands, or can be stored permanently for later use. Below is an example of how these scalars can be stored and used:

```
. scalar A1=r(N)

. scalar A2=r(mean)

. scalar A3=r(sd)

. scalar A4=1345960

. scalar list
          A4 =    1345960
          A3 =  29.761932
          A2 =  38.735886
          A1 =       6086

. scalar A5=(A1/A4)*100000

. scalar list A5
          A5 =  452.16797
```

Stores the value of r(N) from the previous command as a scalar named 'A1'

Stores the value of r(mean) as a scalar named 'A2'

Stores the value of r(sd) as a scalar named 'A3'

Stores a value we assign (1345960 – in this case a population size) as a scalar named 'A4'

Tells Stata to list all of our stored scalars. We can also tell Stata to only list certain scalars if we wish

Creates a new scalar 'A5' that is a rate using the scalar with the N value and pop size

Tells Stata to just list the one scalar 'A5'

The above example is a simple way that scalars can be utilised. They may also be incorporated into foreach loops and in immediate commands (e.g. cci, csi, iri), but those are beyond the scope of this LFF. If you want some more information about using scalars in these instances, please contact Malo University directly for private instruction.

What's the time? Data time!

Your supervisor has noted there seem to be an increasing number of individuals who are having multiple notifications for disease X (a communicable disease) in your region. He wants to know more about those who are having multiple episodes, and if there are any important differences between those who are having multiple episodes compared to those who are only experiencing a single episode of disease. You've been provided with a dataset for confirmed notifications for disease X, and been asked to clean and prepare the dataset for analysis.

Open the dataset malo_university.dta in Stata and start a .do file that you will aggressively annotate and return to Malo University. Open the provided data dictionary to familiarise yourself with the dataset.

Questions:

Q1. How many observations are there in the initial dataset?

Q2. How many unique values are there for the unique person identifier variable, PERSON_ID?

Q3. Are there any exact duplicates in the dataset? If so, drop them like they are hot. Now how many observations and unique values of PERSON_ID exist in the dataset?

Q4. Are there any nonsensical, non-exact duplicates with the same PERSON_ID? What variables would be reasonable to combine with PERSON_ID in the duplicates command to flag observations that might be faulty? Drop any observations that you feel shouldn't be included, recording the relevant identifying information for the observation (PERSON_ID & NOTIF_ID) and any assumptions you are making.

Q5. Are there any dates that don't make sense, either within the same observation or same set of observations for an individual? Drop any observations that you feel shouldn't be included, recording the relevant information and any assumptions you are making. (Hint: a) people having disease after they die? b) different DOB in the same individual? (c) get cordial with _n). How many observations are now in the dataset?

Q6. How many individuals in the dataset have had more than one episode? What is the maximum number of episodes for one individual? (Hint: egen with seq() is your BFF)

Q7. For those with more than one episode, what is the median time and interquartile range (in years) between episodes? (Hint: _n. Bonus marks if you use scalars)

Q8. For those with multiple records, are there any changes to demographics or risk factors over time? For Indigenous status, let's consider that if an individual is identified as Indigenous in any of their records, they are in fact Indigenous.

For diabetes and cardiac disease, let's assume that after they have been recorded as present for an individual, they remain present for any subsequent records. (Hint: create new demographic/risk factor variables and make use of _n). How many records required changing for each of these variables?

Extension questions (not compulsory):

Q9. What proportion of all notifications are repeat notifications?

Q10. What proportion of individuals who have one episode, will go on to have another episode?

Q11. Is there a significant difference between the mean age of those with multiple episodes (at the time of their first episode) compared with those who only experienced a single episode? Report the means and the results of the statistical test you used.

Q12. Compared to those who only have a single episode of disease X, is there a significant difference between the proportions of those who experienced multiple episodes that identify as Indigenous? State any assumptions you are making.

Q13. What proportion of those with multiple episodes are ever-smokers (have been recorded as either a current smoker or ex-smoker in any observation)? Compared to those with only one episode?

(This page is 99% blank)

VI

Summary of other public health activities and experiences

Rheumatic heart disease as a notifiable condition

Background

Rheumatic heart disease (RHD) is a preventable condition that disproportionately affects Aboriginal and Torres Strait Islander people, and is caused by repeated episodes of acute rheumatic fever (ARF). While ARF is a notifiable condition in Queensland, RHD is not notifiable. RHD has recently been legislated as a notifiable condition for all people of all ages in Western Australia, South Australia, and in New South Wales for people younger than 35 years.

The Queensland RHD Register and Control Program (the Register) is funded by both State and Commonwealth governments. One of the functions of the Register is to provide a data repository for the monitoring, reporting, and detection of ARF and RHD. Feedback from the Register manager identified that a legislative requirement for health practitioners to notify cases of RHD could potentially lead to improved case detection, management, and monitoring. A decision was therefore made to scope an assessment process for the inclusion of RHD as a notifiable condition in Queensland.

Project role

I developed a project proposal outlining the assessment and subsequent legislative processes, adopting the Communicable Diseases Network Australia notifiable assessment criteria used to assess conditions for inclusion in the National Notifiable Diseases List, as a guide. The Register manager identified suitable stakeholders and experts to participate in a notifiable status assessment (NSA) panel. I assisted my supervisor in communicating with NSA panel members and organising a teleconference to score RHD against the notifiable assessment criteria. I also communicated with relevant stakeholder groups to invite feedback regarding the potential impact of making RHD notifiable on their work or practice. Following the NSA panel teleconference, I wrote a report summarising the results of the assessment process and stakeholder feedback to provide to the Executive Director, Communicable Diseases Branch.

Lessons learned

This project provided me with valuable experience in the assessment process for deciding whether a communicable disease should be made notifiable, as well as the corresponding stakeholder engagement and legislative processes.

Lookback investigation of a dental clinic

Background

In December 2016, the Queensland Chief Health Officer issued an order under the *Public Health Act 2005* for a dental clinic to suspend practice due to concerns over sterilisation procedures.

The Queensland Government health advice phone service (13 HEALTH) contacted dental clinic patients, advising them to attend their usual medical practitioner and request testing for blood-borne viruses (BBVs). A testing clinic was also temporarily established at a local tertiary hospital for dental clinic patients. The subsequent lookback investigation focused on determining the likelihood of patients acquiring BBVs as a result of their visit to the dental clinic.

Project role

During the initial stage of the investigation, I was a member of the incident working group. To identify patients who were diagnosed with a BBV after their dental visit, I performed initial data linkage of dental patients attending the practice over a three-year-period with all notified cases of hepatitis C, hepatitis B, and HIV in Queensland.

Public health units performed follow-up of cases notified with a BBV after a dental visit to gather information related to risk factors for acquisition. I was a member of the Expert Advisory Group to attribute the likelihood of cases having acquired their infection at the dental clinic.

Lessons learned

I was able to gain an in-depth understanding of lookback investigation processes and the importance of balancing the likely public health benefits and resources required for these types of activities.

WHO Western Pacific Regional Office Consultancy

Background

Mass screening for tuberculosis (TB) is recommended by the World Health Organization in populations where the TB prevalence is greater than 1%. A partnership project between the Centers for Disease Control and Prevention (CDC), World Health Organization Western Pacific Regional Office (WPRO), and local Ministry of Health was established to undertake mass screening for TB and non-communicable diseases (NCDs) on the island of Ebeye, Republic of the Marshall Islands.

Project role

I undertook a consultancy with the Stop TB and Leprosy Unit of WPRO to train local Marshallese workers in data entry and establish measures to improve and check data quality. I made two separate visits to Ebeye, one during the establishment and piloting of the screening project, and the second during the final week of the project. During the initial visit, I assisted in refining the screening questionnaire and identifying issues with data quality. In between visits, I conducted weekly data quality checks and raised any potential issues with the project team on Ebeye. In the second visit, I conducted further data quality checks and audited paper questionnaires against the electronic dataset.

Lessons learned

This project provided me with valuable experience working both cross-culturally and with other organisations. I also was able to further develop my skills in data management and data quality assurance activities. I am hopeful this experience will be of assistance in any future work I undertake in developing countries.